RATIONALE FOR THE DEVELOPMENT OF ONTARIO AIR STANDARDS FOR ACETALDEHYDE

CONSULTATION DRAFT

February 1998

Standards Development Branch
Ontario Ministry of the Environment

Ontario

Executive Summary

The Ontario Ministry of the Environment has identified the need to develop and/or update air quality standards for priority contaminants. The Ministry's Standards Plan which was released in October 1996, identified candidate substances for the development of air standards for the next several years (MOEE, 1996). Acetaldehyde was identified as priority for development based both on its toxicity and the fact that Ontario does not currently have an air quality standard for this substance. This document provides the rationale for recommending an Ambient Air Quality Criterion (AAQC) and a half-hour point of impingement (POI) guideline for acetaldehyde.

Acetaldehyde is an organic chemical which is a gas at ambient temperatures and is widely used in a variety of manufacturing processes. Much of the acetaldehyde in ambient air results from the breakdown of organic pollutants in urban atmospheres. Wood-burning and other incineration processes also contribute substantially. In Ontario, outdoor samples collected in 1992-1993 in Windsor and Hamilton indicated concentrations of acetaldehyde in the range of 2 to 4 $\mu g/m^3$ (micrograms per cubic metre of air; as median of annual average) and those collected in Windsor and in Ottawa in 1994 were between 0.6 to 7 $\mu g/m^3$ (minium and maximum annual averages respectively).

The primary human health effects from short-term (acute) exposure to acetaldehyde, at concentrations in the workplace, are irritation to the eyes, the skin and the respiratory tract. In animals, medium-term (sub-chronic) and long-term (chronic) exposures to acetaldehyde induce varying degrees of inflammation and injury to the tissues lining the nose, larynx and trachea. There is insufficient evidence from human health studies to make a decision regarding human carcinogenicity of acetaldehyde. Results from animals studies indicate that inhalation exposure to acetaldehyde can lead to lesions of the tissues in the upper respiratory tract, which may induce tumour development in the tissues lining the tract.

Ontario does not have air quality standards for acetaldehyde. In developing air quality standards for Ontario, the Ministry of the Environment is reviewing and considering air quality guidelines and standards used by environmental agencies world-wide. Of the criteria reviewed from other agencies none were considered adequate. However, the Ministry has evaluated and accepts the scientific studies which support the development of the Reference Concentration established by the United States Environmental Protection Agency and the 24-hour average chronic Reference Exposure Level established by the State of California. After reviewing additional toxicological information and the similarity of the mode of action and differences in activities of a related compound, formaldehyde, the Ministry considers that the uncertainty factors used to derive exposure limits by the United States Environmental Protection Agency and the State of California are overly conservative.

Based on evaluations of additional toxicological information; similarity of the mode of action and differences in toxicological activities of related compounds; the levels of acetaldehyde measured in

Ontario; modelled ground level concentrations from recent applications for Certificates of Approval; the Ministry is proposing to establish:

- a 24-hour average Ambient Air Quality Criterion for acetaldehyde 500 µg/m^3 (micrograms per cubic metre of air).

- an interim Point of impingement guideline of 500 µg/m^3 (half-hour average concentration). The point of impingement guideline is based on the possibility of the irritant property of acetaldehyde due to short-term exposures and will be used to review and assess applications for Certificates of Approval involving emissions of acetaldehyde from new or modified sources.

Acetaldehyde has been included in the second Priority Substances List to be assessed for its toxicity under the *Canadian Environmental Protection Act* (CEPA). The Ministry will re-evaluate the proposed air quality standards for acetaldehyde at the time the assessment under CEPA is completed.

Table of Contents

1.0 Introduction

Ontario's primary approach to regulating air emissions is based on achieving and maintaining air quality which is protective of human health and the environment. The *Environmental Protection Act* requires all stationary sources which emit or have the potential to emit a contaminant to obtain a Certificate of Approval which outlines the conditions under which the facility can operate.

Compliance with air quality standards and guidelines is one of the criteria used to issue Certificates of Approval. Sources or potential sources of a contaminant are required to control emissions to ensure that the concentration of a contaminant specified by the standard is not exceeded at any point off their property. Dispersion modelling which incorporates detailed engineering calculations is used to relate emission rates from a source to resulting ambient concentrations of a particular contaminant.

The Ministry of the Environment uses a combination of regulatory standards, ambient air quality criteria (AAQCs) and point of impingement (POI) guidelines in reviewing Certificates of Approval (MOEE, 1994a). Point of impingement standards are established under Regulation 346 and can be used directly as enforcement tools as the regulation specifies that a source cannot emit a contaminant at a level which would result in a standard being exceeded at its maximal point of impingement off its property (Section 5(3)). All sources are required to comply with Regulation 346 POI standards unless they are specifically exempted in regulation. As POI standards specified under Regulation 346 apply to all sources, socio-economic issues need to be taken into consideration in their development to ensure that the standards are technically feasible and there is a balance between the benefits and costs of improved ambient air quality.

In addition to POI standards established under Regulation 346, the Ministry also has a larger number of ambient air quality criteria and point of impingement guidelines which are derived from AAQCs. These are used by the Ministry to assess general air quality and to evaluate the *potential* for causing an adverse effect (MOEE 1994). Like POI standards specified in Regulation 346, point of impingement guidelines are also used in Certificates of Approval to approve new and modified emission sources. Once incorporated into a legal instrument like a Certificate of Approval, point of impingement guidelines are legally binding, however unlike Regulation 346 POI standards, they do not automatically apply to existing sources at the time they are promulgated. AAQCs are normally set at a level not expected to cause adverse human health or environmental effects based on continuous exposure. As such, socio-economic factors such as technical feasibility and costs are not explicitly considered when establishing such limits.

Generally, point of impingement standards and guidelines which employ half-hour averaging times are set such that compliance with the standard or guideline will ensure that the Ambient Air Quality Criterion which is based on longer term averaging periods (e.g. 24-hours) will not be exceeded. In certain cases where the effect can occur over short-term exposures, like odours, the

24-hour Ambient Air Quality Criterion and the half-hour point of impingement standard may have the same value.

The Ontario Ministry of the Environment has identified the need to develop and/or update air guidelines/standards for priority toxic contaminants. The Ministry's Standards Plan which was released in October 1996, identified candidate substances for the development of air standards for the next several years. Acetaldehyde was identified as priority for development based both on its toxicity and the fact that Ontario does not currently have an air quality standard for this substance.

2.0 Review and General Evaluation

2.1 General Information

Acetaldehyde (CH_3CHO) at ambient temperatures is a gas. The Chemical Abstracts Service (CAS) identification number is 75-07-0, the Registry of Toxic Effects of Chemical Substances (RTECS) number is AB1925000 and the United Nations Hazardous Material number is UN1089. Acetaldehyde is soluble in water. Its odour is described as suffocating and pungent. The odour threshold for acetaldehyde is 7.8 to 33.3 parts per billion (ppb) or 14 to 60 microgrammes per cubic metre of air ($\mu g/m^3$) (CARB, 1993). Geometric means of odour threshold, based on available data, have been reported to be 50 ppb (90 $\mu g/m^3$) (WHO, 1995) and 67 ppb (120 $\mu g/m^3$) (AIHA, 1989).

In animals and humans, the most noticeable acute effect from short-term exposure to acetaldehyde gas is irritation of the eyes, skin and the upper respiratory tract. Clinical effects of exposure to acetaldehyde vapour include erythema, coughing, pulmonary oedema and narcosis. At high concentrations, paralysis leading to death may occur. In humans, acetaldehyde may facilitate the uptake of other atmospheric contaminants by the bronchial epithelium because of its ciliotoxic and mucus-coagulating effects (by reducing the ability to remove foreign particles). Acetaldehyde is much less irritating than the structurally similar formaldehyde.

Subchronic and chronic exposure of laboratory animals to acetaldehyde has been demonstrated to induce varying degrees of inflammation and injury to the nose, larynx and trachea (ACGIH, 1991; U.S.EPA, 1997). Growth retardation has also been observed in hamsters and rats. Inhaled acetaldehyde has been demonstrated to cause cancer in the upper respiratory tract of animals. Data on the effects of ingested acetaldehyde are limited. A small increase in hyperkeratosis (thickening and hardening) of the forestomach of rats was observed following oral exposures to acetaldehyde at 675 mg/kg/day. A no-observed-effect-level (NOEL) of 125 mg/kg was reported in this study (USNRC, 1981; WHO, 1995). Using a "parallelogram approach" to compare the effects of acetaldehyde with those of formaldehyde by inhalation exposure and with effects of ingested formaldehyde, the adverse effects of ingested acetaldehyde was evaluated and suggested that ingested acetaldehyde was not likely to be carcinogenic (Morris *et. al.*, 1996).

2.2 Sources and Levels

Acetaldehyde is used primarily as a chemical substrate for acetic acid manufacture and in the synthesis of other compounds (e.g., pyridine and pyridine bases, peracetic acid, 1,3-butylene glycol and chloral). It is used in the silvering of mirrors; in leather tanning; as a denaturant for alcohol; in fuel compositions; as a hardener for gelatin fibres; in glue and casein products; as a preservative for fish and fruit; in the paper industry; in the manufacture of cosmetics, aniline dyes, and plastics; and in synthetic rubber (ACGIH, 1991).

Acetaldehyde is a natural product of cotton leaves and blossoms, a component of the essential oil of alfalfa. Acetaldehyde also occurs in food, various fruits, several spices and in oak and tobacco leaves. Acetaldehyde is the immediate metabolite of ethyl alcohol in humans and higher plants (WHO, 1995). Anthropogenic sources include fossil fuel and wood burning operations, as a combustion of plastics, tobacco smoke and degradation of sewage and solid biological wastes. Acetaldehyde is also emitted from industrial processes such as the manufacturing of acetic acid, ethanol, acetone and polyvinyl chloride and vinyl acetate.

According to the California Air Resources Board (CARB, 1993), acetaldehyde formation from the degradation of organic pollutants in urban atmospheres contributes 41-67% of the total atmospheric acetaldehyde. Secondary acetaldehyde formation therefore frequently exceeds direct emissions from combustion sources in urban areas. In addition, the degradation of naturally-occurring ethane contributes a small amount of acetaldehyde to polluted and non-polluted atmospheres. The burning of plant and wood materials (wood in residences, open burning, agricultural burning and wildfires) has been estimated to be the largest contributor of acetaldehyde from stationary sources in California (approximately 60%). Approximately 23% of the total atmospheric acetaldehyde was from on-road vehicles (CARB, 1993). A 1978 study of air emissions in the U.S.A., reported in IARC (1985), listed residential wood burning and coffee roasting as the two major sources of the total atmospheric contribution (approximately 78%). The remainder was from various types of manufacturing facilities.

Monitoring data with short sampling times (<24 hours) from two central Ontario sites, Egbert and Dorset, collected in 1988 indicated low levels of acetaldehyde (mean: approximately 1 $\mu g/m^3$; max.: <3.5 $\mu g/m^3$) (Shepson *et. al*., 1991). Data obtained from Environment Canada, indicated that in 1990, the annual average acetaldehyde concentration in Windsor was 1.3 $\mu g/m^3$ (max.: 4.95 $\mu g/m^3$; min.: 0.36 $\mu g/m^3$) (Environment Canada, 1991). The median concentration of outdoor samples collected in 1992 in Windsor, Ontario was 2.0 $\mu g/m^3$. The outdoor air samples collected in 1993 in Hamilton, Ontario had a median concentration of 2.2 $\mu g/m^3$. The mean concentration values collected in the Windsor study ranged from 1.4 to 3.6 $\mu g/m^3$ (Bell *et al.*, 1994; MOEE, 1994b). In 1994, the annual average concentration in urban Windsor was 2.03 $\mu g/m^3$ (max.: 6.04 $\mu g/m^3$; min.: 0.6 $\mu g/m^3$) whereas in urban Ottawa, it was 2.59 $\mu g/m^3$ (max.: 7.14 $\mu g/m^3$; min.: 0.93 $\mu g/m^3$) (Steer, 1996). Levels in U.S. cities were reported to range from non-detected to 124 $\mu g/m^3$ (IARC, 1985). Detection limits for atmospheric acetaldehyde have been reported to be as low as 0.18 - 90 $\mu g/m^3$ using the high performance liquid chromatography analytical methods or 0.09 - 1.3 $\mu g/m^3$ using the gas chromatography-flame thermionic or flame ionization detection methods (Shepson *et. al*., 1991; WHO, 1995).

An analysis of recent applications for Certificate of Approval in Ontario identified 8 facilities with emissions of acetaldehyde covered by a Certificate. These approvals were for emissions from paint, photo products and chemical plants. The median Ground Level Concentration estimated by Regulation 346 dispersion modelling for all 8 sources was approximately 27 $\mu g/m^3$. The maximum and minimum were 494 and 0.007 $\mu g/m^3$, respectively.

Based on the 1993 National Pollutant Release Inventory from Environment Canada, 164 tonnes of the total national release (197 tonnes) of acetaldehyde was to the air (NPRI, 1993). The release of acetaldehyde to the air of Ontario totalled 52.6 tonnes. Releases from mobile sources and fuel distribution operations in Ontario were 1,342 tonnes whereas on-road motor vehicle emissions amounted to 1,142 tonnes. In 1994, total national atmospheric acetaldehyde releases were 133 tonnes (NPRI, 1994). Of these, 44.56 tonnes were released in Ontario, primarily from textile industries. The 1994 atmospheric releases from mobile sources and fuel distribution operations and on-road motor vehicle emissions in Ontario were basically unchanged at 1,370 and 1,164 tonnes, respectively. In 1995, the NPRI reported a national atmospheric release of acetaldehyde to be 289 tonnes (NPRI, 1995). Ontario atmospheric acetaldehyde releases were reported to be 51.7 tonnes. The releases of acetaldehyde to the air of Ontario appeared to vary within a narrow range over the past three years.

3.0 Development of Ambient Air Quality Criteria for Ontario

3.1 Discussion of Toxicological Effects

The most noticeable effect of acute exposure to acetaldehyde is irritation to the eyes, nose and the respiratory tract. This effect usually occurs at occupational exposure concentrations. The primary effect of mid- or long-term exposures to acetaldehyde by inhalation is tissue damages to the upper respiratory tract. In animal trials these damages are manifested as degeneration of the olfactory and respiratory epithelia. Furthermore, chronic exposure to acetaldehyde through inhalation has been associated with tumour development in the respiratory tract of animals. At present, the carcinogenic effect of inhaled acetaldehyde in humans cannot be adequately assessed because of an insufficient database. Based on these adverse effects of acetaldehyde, both the noncarcinogenic and carcinogenic endpoints should be considered in evaluating the scientific criteria for this chemical in guideline development.

3.1.1 Discussion based on the noncarcinogenic effect of acetaldehyde

The primary effect of acute exposure to acetaldehyde vapours is irritation to the eyes and mucous membranes as well as reddening of the skin. Acetaldehyde may also induce pulmonary oedema, headache and sore throat. In clinical studies, exposures of short duration to acetaldehyde caused some degree of eye irritation and mild irritation of the upper respiratory tract at concentrations above 90 mg/m^3 and 240 mg/m^3, respectively; long-term exposure may cause dermatitis and conjunctivitis (ACGIH, 1991; WHO, 1995).

The acute toxicity of acetaldehyde is considered low in animals exposed through inhalation. The LC_{50} (0.5- and 4-hour) found in rats and Syrian hamsters ranged from 24 - 37 g/m^3 (WHO, 1995). Subchronic treatment of male rats to acetaldehyde vapours at 437 mg/m^3 for 8 hours/day, 5 days/week for 5 weeks resulted in hyperplasia of the olfactory epithelium, nasal inflammation as well as increased residual volume and functional residual capacity, suggesting unspecified damage of the distal airways (cited in WHO, 1995).

In a subchronic (mid-term) study, fifty male and fifty female adult albino SPF Wistar rats were treated with varying concentrations (0, 400, 1000, 2200 or 5000 ppm or 0, 720, 1800, 3960 or 9000 mg/m^3) of acetaldehyde for 6 hours/day, 5 days/week for 4 weeks (Appelman *et. al*., 1982). Animals developed severe dyspnoea (shortness of breath) and excitation during the first half hour of exposure to acetaldehyde at 9000 mg/m^3. Growth retardation was observed in male animals in the three high-dose (1800 - 9000 mg/m^3) groups and in females of the highest dose group only. Significant decreases in liver weights in animals of both sexes and increases in lung weight in male rats were observed at the 9000 mg/m^3 dose. Lesions of the larynx and trachea occurred at the 3960 and 9000 mg/m^3 doses. Dose-related pathological damages of the nose occurred at every dose level. The most severe lesion was located in the dorsal part of the nose which is covered with olfactory epithelium, except the most anterior part. Damage ranged from loss of microvilli, accompanied by thinning and disarrangement of the epithelium and occasional loss of the sensory cells at the 400 ppm (720 mg/m^3) dose, to severe atrophy of the epithelium at the highest dose. The olfactory cells also showed focal hyperplasia and squamous metaplasia at the two high doses. Degenerative changes of the respiratory epithelium were observed at the three high-dose levels and the affected areas were focal in that the posterior part of the nose was more severely affected than the anterior part. In this mid-term (4-week) study, 400 ppm (720 mg/m^3) appeared to be the lowest observed effect dose.

In another subchronic study in which eighty male albino SPF Wistar rats were exposed to acetaldehyde at 0,110, 150 or 500 ppm (0, 198, 270 or 900 mg/m^3) by inhalation for 6 hours/day, 5 days/week for 4 weeks (Appelman *et. al*., 1986). There were three dose schedules. In schedule one, animals were exposed without interruption. In schedule two, the exposures were for two 3-hour periods each day, interrupted by a treatment-free period of 1.5 hours between the first and the second exposures. In schedule three, the exposure profile was similar to schedule two, the exposures were interrupted and superimposed with 5-minute periods of six times the basic concentration with a frequency of four peak exposures per the 3-hour period. Control animals received fresh air only. Only treatment with acetaldehyde at peak exposures (5400 plus 900 mg/m^3) induced irritation and excitation and reduced body weight gain. Exposure to acetaldehyde at 500 ppm (900 mg/m^3) induced lesions in the nose. The interruption of a daily exposure period at the same concentration by an 1.5 hours exposure-free period or by the same interruption schedule and concentration and also superimposed with 5-minute peak exposure concentrations (3000 ppm or 5400 mg/m^3), did not affect the potency of the nasocytotoxicity of this aldehyde in rats. Lesions were found only in the nose of the exposed animals. Degeneration was located in the dorsal part of the nose which, except the most anterior part, is covered with olfactory epithelium. The damages were characterized by loss of microvilli accompanied by

thinning, disarrangement, and individual necrosis of the epithelium. Lesions were not observed in animals treated with 150 ppm (270 mg/m^3) or 110 ppm (198 mg/m^3) plus peak concentration of 660 ppm (1188 mg/m^3), with or without an interruption period. A "no-toxic-effect-level" of 150 ppm (270 mg/m^3), based on olfactory epithelium degeneration, was suggested.

The histopathological effect of exposure to acetaldehyde vapour was studied in hamsters (Kruysse *et. al*., 1975). Young male and female golden Syrian golden hamsters, forty animals of each sex, were exposed to acetaldehyde vapour at 0, 390, 1340 and 4560 ppm (0, 702, 2412 and 8208 mg/m^3) for 6 hours/day, 5 days/week for a period of 90 days. Growth retardation occurred in animals of both sexes exposed to the highest concentration throughout the experiment. Treatment-related histopathological changes were observed only in the respiratory tract. Changes in the nasal cavity, larynx, bronchi and lungs were observed at the highest concentration only whereas changes in the trachea occurred at the two highest dose. Lesions in the nasal cavity included rhinitis, necrosis and metaplasia of the respiratory and olfactory epithelium. At the highest exposure concentration, serious damage to the tracheal epithelium was observed. Large areas of the tracheal mucosa surface were covered with stratified squamous epithelium, which was often heavily keratinized. Hyperplastic and metaplastic stratified epithelium were observed in the main stem bronchi of some male and female animals at the highest dose. Stratified epithelium was noticed in some animals exposed to the 1340 ppm (2412 mg/m^3) dose of acetaldehyde. No observed effects were observed at the 390 ppm (702 mg/m^3) dose group. This concentration could be regarded a "no toxic effect concentration".

Upper respiratory tract damage was also observed from a chronic study in Syrian golden hamsters which were treated with varying concentrations (0, 2500 - 1650 ppm or 0, 4500 -2970 mg/m^3 at the different stages of the exposure duration) of acetaldehyde vapour, 7 hours/day, 5 days/week for 52 weeks. The dosages were reduced several times due to considerable growth retardation and to avoid early mortality. Animals were sacrificed after 81 weeks. Five hundred and four animals for each sex were used. Control animals were exposed to air only. Pathological changes induced by acetaldehyde were observed in the nose, larynx and the trachea. Nasal changes included rhinitis, thinning and degeneration of the olfactory epithelium and thickening of the submucosa. Metaplastic stratified squamous epithelium on the naso-maxillary turbinates and on the anterior part of the nasal septum was also found. The lesions in the upper segments of the respiratory tract had disappeared completely or markedly reduced in severity and extent after a recovery period of 29 weeks (Feron *et. al*., 1982).

A similar study was performed to study the effect of acetaldehyde following discontinuation of exposure. Four hundred and twenty male and 420 female adult albino Wistar rats were exposed to various concentrations of acetaldehyde (0, 750, 3000/1500 ppm or 0, 1350, 2700, 5400/2700 mg/m^3 at different stages of the exposure period) by inhalation for 6 hour/day, 5 days/week for 52 weeks (Woutersen and Feron, 1987). Animals were used for pathological studies at the end of the 52-week treatment period, or after a further treatment-free period of 26 or 52 weeks. At the end of the treatment period, degeneration of olfactory epithelium was observed at all dose levels and focal hyperplasia were also evident. Hyper- and metaplasia of the respiratory epithelium was

seen at the highest dose only. During or after the recovery periods (26-week or 52-week), damaged olfactory epithelium showed signs of regression (regeneration) at low and mid-dose levels, whereas the recovery of the badly damaged respiratory epithelium in animals exposed to high dose was not evident. Nasal tumours found were similar to those observed in lifetime studies, suggesting that hyperplasia and metaplasia may have progressed into neoplastic formation during the treatment-free periods.

Results from these rat and hamster studies suggest that a no toxic effect level of 150 ppm (270 mg/m^3) for rats and a no toxic effect level of 390 ppm (702 mg/m^3) for hamsters, based on damages to the upper respiratory tract following inhalation exposure to acetaldehyde, could be identified. It would appear that damages to the upper respiratory tract is the most sensitive and consistent endpoint to be considered for the development of noncancer-based criteria.

There are reports of reproductive, developmental, neurological (through autonomic nervous system on respiration and cardiovascular functions), and immunological effects of acetaldehyde in animals. The routes of exposures were usually carried out by systemic applications (e.g. intraperitoneal, intravenous or amniotic injections). Dose-related responses were observed in some of these studies, however, data were not adequate for assessing the significance of these effects in humans. In the case of two inhalation studies in rats and mice, a decrease in respiratory rate was observed at a very high dose of 5,000 mg/m^3 (cited in WHO, 1995). In other instances, the effects were biochemical changes and the significance of these changes is difficult to assess. As well, the exposure concentrations were much higher than those which caused damage to the upper respiratory tract. For example, alteration in neural membrane enzyme (Na^+-K^+-ATPase) activity in rat cerebral cortex was demonstrated. Animals were exposed to acetaldehyde at 0.3 mmol/L (or 8810 ppm or 13215 mg/m^3) for 80 min. (4 x 20 min.) for 2 - 21 weeks. Increases in enzyme activities ranged from10 to 20 % over the control were observed (Shiohara *et. al.*, 1985).

3.1.2 Discussion based on the genotoxic and carcinogenic effect of acetaldehyde

Genotoxic effects of acetaldehyde

Cytogenetic studies using animal and human tissues suggest that acetaldehyde is a mutagen with clastogenic (chromosome-breaking) properties. Results of the evaluation of the mutagenic potential of acetaldehyde using bacterial tests, with or without metabolic activation, have been mostly negative. Injection of acetaldehyde in ethanol into Drosophila induced sex-linked recessive lethal mutations. In the absence of metabolic activation, acetaldehyde induced: forward mutation in cultured mouse lymphoma cells and in human lymphocytes; sister chromatid exchange in Chinese hamster ovary cells and human lymphocytes; aneuploidy (hypodiploidy in Chinese hamster cells); chromosome aberration in Chinese hamster ovary cells, human lymphocytes, and skin fibroblast of rats. These cytogenetic abnormalities may be attributable to the clastogenic properties of acetaldehyde, and thus, may underline the carcinogenic effect of this compound (cited in Dellarco, 1988; WHO, 1995; also see Appendix 7.9 for summary table of mutagenicity

studies). Acetaldehyde has been demonstrated to induce DNA-DNA interstrand cross-links in calf thymus tissues, human bronchial epithelial cells, leukocytes and lymphocytes; DNA single-strand breaks in Chinese hamster ovary cells, rat hepatocytes, human bronchial epithelial cells and human leukocytes; DNA single- and double-strand breaks in human lymphocytes (Singh and Khan, 1995); DNA-protein cross-links in calf thymus nucleohistones and human bronchial epithelial cells (WHO, 1995). Acetaldehyde, like other aldehydes (formaldehyde, acrolein; Grafström, 1990), is capable of inducing accelerated cross-linked envelope formation in human bronchial epithelial cells and this may result in initiating squamous differentiation of these cells (Saladino *et. al*., 1985). From an enzymic perspective, acetaldehyde inhibits O^6-methylguanine transferase activity in *in vitro* (rat and human liver) and *in vivo* (rat liver) studies (Espina et. al., 1988) and also in cultured human skin fibroblasts (Grafström *et. al*., 1994). O^6-methylguanine transferase is an enzyme responsible for the repair of DNA from adduct formation. Acetaldehyde has also been demonstrated to increase the frequency of 6-thioguanine resistance mutation in cultured human skin fibroblasts and this mutagenic potency is several-fold higher than that observed with formaldehyde or acrolein at similar colony survival levels (Grafström et. al., 1994). This high mutagenic efficiency of acetaldehyde, together with its ability to induce several types of DNA and cytogenetic damages in various cell culture systems (e.g. human epithelial cells and skin fibroblasts and lymphocytes), have been suggested to be associated with the development of tumours.

Carcinogenicity in humans

Results from animal studies indicated that exposure to acetaldehyde by inhalation may lead to carcinogenic development in the upper respiratory tract. Since the epidemiological evidence is considered to be inadequate, this compound is currently classified as a probable human carcinogen based upon the animal carcinogenicity data (IARC, 1987; U.S.EPA, 1997). There was only one epidemiological study which indicated that exposure to acetaldehyde may be associated with an increase in the incidence rate of total cancers in acetaldehyde production workers as compared with the general population (Bittersohl, 1974, as cited in U.S.EPA, 1997, 1986; IARC, 1987). The cancer types reported were squamous cell carcinoma in the bronchi and of the mouth cavity, adenocarcinoma of the stomach and of the caecum. Because the incidence rate was not age adjusted, and because of other major methodological limitations (including concurrent exposure to other chemicals and cigarette smoke exposure; short duration; small number of subjects; and lack of information on subject selection in the cohort; age and sex distribution), this study is considered inadequate for evaluating the carcinogenicity of acetaldehyde in humans.

Carcinogenicity in animals

There is sufficient evidence to consider acetaldehyde as an animal carcinogen based on the classification scheme employed by IARC and the U.S.EPA (IARC, 1987; U.S.EPA, 1997). Data from animal studies indicate that exposure to acetaldehyde by inhalation, results in development of squamous cell carcinoma in the respiratory epithelium and adenocarcinoma of the olfactory epithelium of the nose as well as squamous metaplasia of the larynx of rats.

In a 28-month study, 420 male and 420 female Wistar rats were initially exposed to acetaldehyde at concentrations of 0, 750, 1500 or 3000/1000 ppm (or 1365, 2730, 5460/1800 mg/m^3) (Woutersen *et. al*. 1986). The 3000 ppm (5460 mg/m^3) concentration was reduced to 1000 ppm (1800 mg/m^3) because severe growth retardation and early mortality occurred at this high concentration. Nasal adenocarcinomas (the majority type) and squamous cell carcinoma were observed at dose levels where a strong dose-response relationship for other cytotoxic endpoints, such as epithelial hyperplasia, was observed. Incidence of tumours at 750 and 1500 ppm (or 1365 and 2730 mg/m^3) for male animals was 33% and 77% and for female animals was 13% and 64%, respectively.

Feron *et al*. (1982) exposed Syrian golden hamsters to decreasing concentrations of acetaldehyde for 52 weeks, with observations continuing up to 81 weeks. The initial concentration of 2500 ppm (4500 mg/m^3) was gradually decreased to 1650 ppm (2970 mg/m^3) due to increased mortality at the high dose. A statistically significant increase in laryngeal carcinoma in male hamsters was observed and tumours were also found in the nose of the tested animals. Feron *et. al*. (1982) also demonstrated that after a recovery period following cessation of treatment with acetaldehyde, the lesions in the upper respiratory tract had either completely disappeared or at least the severity and extent had markedly reduced; however, the acetaldehyde-induced hyper- and metaplasia were persistent and irreversible. Regeneration of damaged olfactory epithelium was also observed in rats treated with cytotoxic doses (750 and 1500 ppm or 1350 and 2700 mg/m^3) of acetaldehyde; however, progression of the hyper- and metaplastic tissues into neoplastic tissues or tumours was irreversible (Woutersen and Feron, 1987).

Mechanisms of acetaldehyde carcinogenesis

Carcinogenesis is widely considered a multistage process driven by carcinogen-induced genetic or epigenetic damage in susceptible cells. The activation of proto-oncogenes and/or inactivation of tumour suppressor genes, as a result of these damages, will then lead to a selective growth and clonal expansion of these cells (Harris, 1991). The stages of carcinogenesis in humans involve initiation, promotion, conversion and progression. Acetaldehyde has been described as a weak tumour initiator as well as a strong tumour promoter in animal studies (Feron *et. al*., 1982; Woutersen *et. al*., 1986). Thus, understanding the mechanism of acetaldehyde-induced carcinogenesis may provide weighted evidence in the assessment of carcinogenic risk in the exercise of criteria development for this compound.

Actions on genetic material

Unlike aldehydes such as acrolein and formaldehyde, information on the carcinogenic mechanism of acetaldehyde is limited. Animal inhalation studies suggest that acetaldehyde alone can induce squamous cell carcinoma in the respiratory epithelium and adenocarcinoma of the olfactory epithelium (Feron *et. al*., 1982; Woutersen *et. al*., 1986). The mutagenic and clastogenic properties of acetaldehyde may account for its initiator activity. This notion can be supported by the nature of its chemical and molecular action on genetic materials. Acetaldehyde is electrophilic

and has a saturated chemical structure which is reactive towards the thiol or the amino group of macromolecules. The alkylating properties of acetaldehyde may be responsible for the inhibition in the activity of the DNA repair enzyme, O^6-methylguanine transferase, and therefore induces the O^6-thioguanine resistance mutation significantly in cultured human skin fibroblasts and in rat and human liver extracts. O^6-methylguanine transferase reverses alkylated DNA adducts induced by external agents or from endogenous mutations (Espina *et. al.*, 1988*;* Grafström *et. al*., 1994). The frequency of acetaldehyde-induced O^6-thioguanine resistance mutations in human skin fibroblasts is several-fold higher than that caused by formaldehyde or acrolein at similar cultured colony survival levels (Saladino *et. al.,* 1985; Grafström *et. al*., 1994).

Acetaldehyde can also react with DNA to form DNA-DNA cross-links or DNA-protein cross-links, likely through Schiff base formation, in cultured human skin fibroblasts and in human lymphoma cells (Dellarco, 1988; Grafström *et. al*., 1994; Costa *et. al.,* 1997); in nasal mucosal homogenates of male Fischer-344 rats *in vitro* and in respiratory and olfactory mucosa of rats *in vivo* following repeated inhalation treatment with acetaldehyde (Lam *et. al*. (1986). DNA double-strand break in human epithelial cells (Grafström *et. al*., 1994) or single- and double-strand breaks in human lymphocytes (Singh and Khan, 1995) have been reported. As discussed earlier, sister chromatid exchange has been demonstrated in various cell models (WHO, 1995). These cytogenetic effects of acetaldehyde may be associated with increases in mutation frequency, possibly leading to tumour formation (Harris, 1991; Grafström *et. al*., 1994).

Tumour promotion effects

Acetaldehyde has been described as a strong tumour promoter in animal studies (Feron *et. al*., 1982; Woutersen *et. al*., 1986). Syrian golden hamsters were exposed to decreasing concentrations (2500 -1650 ppm or 4500 -2970 mg/m^3) of acetaldehyde by inhalation with or without concomitant intratracheal instillations of benzo(a)pyrene (18.2 or 36.4 mg) or subcutaneous injections of diethylnitrosamine (2.1 µL of a 0.065% solution per hamster) for 52 weeks. There were 30 male and 30 female animals in each test group and 18 male and female animals in each control group. Control animals received fresh air or in combination with the 0.9% saline vehicle solution. Acetaldehyde markedly increased the incidence of tracheobronchial tumours initiated by the high dose of benzo[a]pyrene (incidence of tumours: 11 in males and 3 in females for benzo(a)pyrene alone vs 19 males and 12 females for acetaldehyde combined with benzo(a)pyrene) and also shortened the latent period for carcinoma development but did not enhance diethylnitrosamine-initiated tumours in the respiratory tract (Feron *et. al.*, 1982). Most of these tumours were of the squamous cell carcinoma and adenocarcinoma types. This enhanced response was not observed in animals treated with acetaldehyde and the low dose of benzo(a)pyrene. Combined benzo[a]pyrene/acetaldehyde treatment did not enhance the tumour response of the nose, larynx or lungs as compared with treatment with benzo[a]pyrene or acetaldehyde alone. However, treatment with acetaldehyde alone induced development of hyperplasia, metaplasia and tumours in the nose and the larynx. Most of the tumours found included adenoma, adenocarcinoma and anaplastic carcinoma in the nose; carcinoma *in situ*, squamous cell carcinoma and adeno-squamous carcinoma in the larynx (e.g. 7% and 26% in males

and 4% and 20% in females for the nose and larynx tumours, respectively). The acetaldehyde(1500 ppm or 2700 mg/m^3)-enhanced development of tracheobronchial tumours (adenocarcinoma and squamous cell carcinoma) initiated by intratracheal instillation of high dose (56 mg) of benzo(a)pyrene in Syrian golden hamsters (Feron, 1979) was observed in an earlier study. However, no tumours were found in the respiratory tract of animals treated with acetaldehyde alone. This was attributed to the lower concentration of acetaldehyde used in this earlier experiment.

In hamsters and rats, acetaldehyde induced cytotoxic lesions (degeneration of the olfactory epithelium, inflammation, hyperplasia and metaplasia) in the upper respiratory tract and these lesions were reversible or reduced after a recovery period (Feron *et. al.,* 1982; Woutersen and Feron, 1987). This process of recurrent tissue damage and repair as a result of acetaldehyde exposure may promote the formation of tumour induced by endogenous or exogenous carcinogens.

At the cellular level, acetaldehyde, like formaldehyde and acrolein, has been demonstrated to increase the formation of cross-linked envelopes in normal human bronchial epithelial cells, a late event in the terminal differentiation of epithelial cells and considered a marker for squamous differentiation in cultures (Saladino *et. al*., 1985; Grafström *et. al*., 1994). It has been suggested that the mechanism for this accelerator effect of acetaldehyde in squamous differentiation (through formation of cross-linked envelopes) is different from that of the potent tumour promoter, phorbol ester (12-*O*-tetradecanoylphorbol-13-acetate). Acetaldehyde promotes increases in the formation of cross-linked envelopes without changing cellular morphology and its mechanism of action is similar to that of the calcium ionophore, i.e. by increasing cytosolic free calcium (Saladino *et. al.,* 1985; Grafström *et. al*., 1994).

In summary, there is sufficient evidence to support the notion that inhaled acetaldehyde is carcinogenic to animals. The most predominant types of tumours are the squamous cell carcinoma of the respiratory epithelium and adenocarcinoma of the olfactory epithelium in the nose. Tumours may be initiated through mutagenic or clastogenic changes in the DNA matrix subsequent to acetaldehyde exposure. On the other hand, acetaldehyde may promote the progression of hyper- or metaplastic tissue into neoplasia, leading to tumour development. In view of these effects, acetaldehyde has been described as a tumour initiator (weak) as well as a promoter (strong).

3.2 Review of Existing Air Quality Guidelines

A summary of various agencies' air quality guidelines for acetaldehyde is presented in Table 1. Detailed agency-specific summaries are presented in the Appendix of this report. Currently there is no Ontario Ambient Air Quality Criterion for acetaldehyde. Among the selected agencies, only four have guidelines for this compound. The U.S.EPA, states of California and Massachusetts have guidelines based on the carcinogenic and the noncarcinogenic effects of acetaldehyde. The air concentrations for the lifetime additional cancer risk range from 0.4 to 0.5 µg/m^3 at a risk level

of 10^{-6}. The noncancer-based criteria range from 4.89 to 9 µg/m^3. The guidelines of New York State are derived from occupational exposure limits.

3.2.1 Guidelines based on a noncarcinogenic endpoint

Certain jurisdictions, such as the Commonwealth of Massachusetts and New York State, have developed short-term limits which are based on extrapolation from occupational standards. In New York, the long-term guideline is also based on extrapolation from the occupational standards. These occupational exposure limits were developed by ACGIH (1991) to prevent eye irritation and damage to the respiratory tract using studies of acetaldehyde effects on humans. The original ACGIH values were 100 ppm or 180 mg/m^3 (TLV-TWA) and 150 ppm or 270 mg/m^3 (STEL). The difference in the final values of the criteria of the states of Massachusetts and New York arose from the discrepancies in the application of uncertainty factors when the occupational exposure limits were used for environmental regulation purposes.

The U.S.EPA (19967) derived an inhalation Reference Concentration (RfC) which represents protection from the noncancer adverse effects of acetaldehyde. This criterion was derived based on a subchronic study conducted by Appelman *et. al*. (1986). In this study, a no-observed-adverse-effect level (NOAEL) of 150 ppm (270 mg/m^3) was established based on the degeneration of nasal olfactory epithelia in rats. This toxic endpoint was considered to be the most sensitive indicator of adverse effects in short- and long-term studies. This NOAEL of 150 ppm (270 mg/m^3) was converted to a human equivalent NOAEL of 8.7 mg/m^3 in the extrathoracic area by dosimetric conversion (see Appendix 7.1). This converted exposure level was further adjusted by 1000 to account for uncertainties in extrapolation from animal models to humans and for extrapolation from data from a short-term study to making a prediction on long-term exposure. The RfC was calculated to be 9.0 µg/m^3. The State of California (CARB, 1993) concurred with the U.S.EPA on this risk assessment procedure and adopted this value for their inhalation chronic Reference Exposure Level.

Based on data from the same animal study (Appelman *et. al*., 1986), WHO and its associates (1995) have developed a tolerable concentration of 0.3 mg/m^3 (300 µg/m^3) for acetaldehyde. This value was derived from the NOAEL of 275 mg/m^3 divided by an uncertainty factor of 1000 (to account for intra- and interspecies differences, lack of long-term information and carcinogenicity associated with irritation, i.e. possible existence of a threshold).

Table 1. Summary of Existing Air Quality Guidelines[a] for Acetaldehyde

Agency, Date[b]	Guideline(s)[c]		Comments
U.S.EPA (IRIS) 1991	No ambient air exposure limits available		
	9 µg/m^3	(reference concentration)	based on the damage to the nasal olfactory epithelia.
	5 µg/m^3 0.5 µg/m^3	(lifetime exposure) (lifetime exposure)	$1*10^{-5}$ extra cancer risk $1*10^{-6}$ extra cancer risk both are based on unit risk of $2.2*10^{-6}$ tumours/(µg/m^3)
California 1992	9 µg/m^3	(inhalation reference exposure level)	Inhalation Reference Exposure Level to be used for evaluation of non-cancer risk; adopted from the RfC of the U.S.EPA
	4 µg/m^3 0.4 µg/m^3	(lifetime exposure) (lifetime exposure)	$1*10^{-5}$ excess cancer risk $1*10^{-6}$ excess cancer risk both are based on unit risk of $2.7*10^{-6}$ tumours/(µg/m^3)
WHO 1987	none		
Netherlands 1987	none		
Sweden	none		
New York 1990	43,000 µg/m^3 430 µg/m^3	(1-hour average) (annual average)	1-hour average, based on occupational exposure limits annual average based on individual occupational limits
Massachusetts 1990	4.89 μg/m^3	(24-hour ceiling) limit	24-hour average, based on occupational exposure limits
	0.44 µg/m^3	(allowable ambient limit)	$1*10^{-6}$ extra cancer risk based on unit risk of $2.26*10^{-6}$ tumours/(µg/m^3)
Ontario (current)	none		

a. Guidelines in this table can refer to: guidelines, risk-specific concentrations based on cancer potencies, and non-cancer-based reference concentrations.

b. Date here refers to when the health-based guideline background report or original legislative initiative was issued. Sources were the respective agency documents.

c Conversion of units for the air concentration for Ontario is based on 1 atmosphere of pressure and 10°C. 1.0 µg/m^3 = 0.527 ppb; 1 ppb = 1.897 µg/m^3. Depending on the temperatures employed, conversion of units by the different agencies may vary.

3.2.2 Guidelines based on a carcinogenic endpoint

The U.S.EPA, California and Massachusetts have used the animal study data of Woutersen *et. al*. (1984; 1985; 1986) to obtain upper 95% confidence limits on inhalation unit risk estimates of 2.2 x 10^{-6}, 2.7 x 10^{-6}, and 2.26 x 10^{-6} tumours per ($\mu g/m^3$) for acetaldehyde, respectively, using linearized multi-stage models. The unit risk estimates represent an additional risk, during lifetime exposure, of 1 in 100,000 for 4 to 5 $\mu g/m^3$ and 1 in 1,000,000 for 0.4 to 0.5 $\mu g/m^3$ (see Table 1). These three agencies considered that the carcinogenicity of acetaldehyde is associated with the mutagenic potential of this compound and they have discounted the consideration of a threshold below which tumour development will not occur. Among these agencies, only California has incorporated surface area conversion for animal to human extrapolation and considered that male rats are more sensitive than female rats for nasal tumour development (California EPA, 1993).

The WHO (1995) has estimated risk-specific concentrations for inhaled acetaldehyde to be 11 - 65 $\mu g/m^3$ at a lifetime excess cancer risk level of 10^{-5}. These values were derived from the unit risk estimates based on the lower 95% confidence limits using the data of Woutersen *et. al*. (1986). A linearized multi-stage model was used to calculated the unit risk factors but a body surface area correction was not applied. Animals from the highest dose group were not considered because of early mortality.

3.3 Evaluation of Information for Criteria Development

Recommendations for new or revised Ontario Ambient Air Quality Criteria and Point of Impingement standards are based on initial analyses of guidelines from various agencies and on the scientific information, such as cancer and noncancer endpoints, supporting these guidelines. Using a weight-of-evidence approach, the guidelines of the various agencies together with relevant available information, (including recent scientific research and science/policy information, ambient atmospheric and monitoring levels, as well as frequency of applications for operating permits and the estimated emission levels associated with these permits) are reviewed by MOE staff to derive a final guideline recommendation.

3.3.1 Review of guidelines from other agencies

Based on a review of criteria based on a noncarcinogenic endpoint from the various agencies, the Reference Concentration (RfC) of the U.S.EPA and the chronic Reference Exposure Level (REL) of the California Department of Health Services (CDHS) are considered to have a scientifically reasonable rationale. For the carcinogenicity-based guidelines, those established by California (CAPCOA, 1993) and Massachusetts (Commonwealth of Massachusetts, 1990) have received the widest public review, including reviews by government, corporate and non-governmental organization scientists and risk assessors. They are supported by similar use of information and methodology employed by the U.S.EPA to derive similar risk estimates. Thus, they are reflective of broad consensus on the issue of carcinogenicity-based, air quality guidelines. Although the unit risk estimates are slightly different, they both indicate an ambient air exposure levels of 4 and 5

μg/m^3, for additional lifetime carcinogenic risk levels of 10^{-5} and 10^{-6} respectively. These values are in close agreement with those estimated by the WHO (1995)

3.3.2 Review of information on adverse effects

After reviewing the scientific rationale documents from the various agencies and the additional biochemical and toxicological information from recent literature, it is apparent that the occurrence of lesions of the nasal epithelia (a noncarcinogenic endpoint) and the development of tumours in the nasal epithelia (a carcinogenic endpoints) are both dose-related and site-specific to the upper respiratory tract. It is therefore necessary to examine, in more details, the nature of these toxicological effects and the possible mechanisms underlying them in order to provide an appropriate scientific rationale for the recommended standard and guidelines.

Noncarcinogenic effect basis

Data from animal studies strongly indicate that inhaled acetaldehyde is detrimental to the upper respiratory tract. There are a few common observations. In rats and hamsters, subchronic or chronic inhalation exposure to acetaldehyde induced lesions to the olfactory and respiratory epithelia of the nose or to a lesser extent, the larynx. Short interruption of the daily exposures did not appreciably affect the potency of a toxic dose of acetaldehyde. Both regressive and progressive changes of hyperplastic and metaplastic lesions were observed. Following a long recovery period after the cessation of the acetaldehyde exposure, regeneration of the damaged epithelium, particularly the olfactory epithelium, could occur. Under the condition of long-term treatment at high doses, the hyperplastic and metaplastic tissues could also progress irreversibly into neoplasia which may lead to the development of tumour, e.g. squamous cell carcinoma of the respiratory epithelium and adenocarcinoma of the olfactory epithelium. A NOAEL of 150 ppm (270 mg/m^3) was suggested based on cytotoxic damages to the upper respiratory tract of rats (Appelman *et. al*., 1986). The RfC developed by the U.S.EPA was derived from this NOAEL and this agency criterion may be an appropriate reference for guideline development.

Carcinogenic effect basis

Acetaldehyde is found to be carcinogenic to animals. There are two possible mechanisms underlying the carcinogenicity of acetaldehyde, namely tumour initiation and tumour promotion. Acting as a **tumour initiator,** acetaldehyde may induce tumourigenic events through its actions on the genetic material, e.g. aneuploidy (hypodiploidy in Chinese hamster cells) formation, sister chromatid exchange, DNA-DNA or DNA-protein adducts, DNA strand breaks. These premutation events may predispose DNA to alterations and lead to mutation of somatic cells. For example, point mutation in the rat *p53* complementary DNA sequence of the tumour suppressor gene induced by chronic exposure to formaldehyde (15 ppm or 27 mg/m^3) was suggested to result in formation of squamous cell carcinoma in the respiratory epithelium (Recio *et. al.,* 1992) (mutations of the *p53* gene are commonly found in human tumours). Both formaldehyde and acetaldehyde have been demonstrated to induce sister chromatid exchange and DNA-protein

cross-links in cultured cells except that formaldehyde is more potent than acetaldehyde (Dellarco, 1988).

If acetaldehyde-induced point mutations do occur and lead to the development of nasal tumours in rats and nasal and larynx tumours in hamsters, then one can anticipate that a threshold dose does not exist for this compound. It is also conceivable that the tumourigenic effects of acetaldehyde will be linear to the range of doses extrapolated down from the point of departure (from the lowest experimental dose). Thus, applying the linearized multi-stage model and using the data from Woutersen *et. al* (1984, 1985; 1986), the U.S.EPA, States of Massachusetts and California have obtained incremental cancer risk estimates of $2.2 \times 10^{-6} \bullet(\mu g/m^3)^{-1}$, $2.26 \times 10^{-6} \bullet(\mu g/m^3)^{-1}$ $2.7 \times 10^{-6} \bullet(\mu g/m^3)^{-1}$, respectively. The U.S.EPA employed two sets of data for its cancer risk estimation. One set of data came from a 27-month study (Woutersen *et. al*., 1985) and the other set was based on a one-year treatment and a half-year recovery study (Woutersen *et. al*., 1984). Both California and Massachusetts considered the 28-month study (Woutersen *et. al*., 1986) a valid lifetime study and selected the male data for their unit risk estimation for the fact that the male was more sensitive to the carcinogenic activity of acetaldehyde. California included both types of tumour in their estimation and also applied a metabolic conversion factor for animal to human data extrapolation. Massachusetts selected the data on adenocarcinoma of the olfactory epithelium for the sensitivity towards this type of tumour. The rationale underlying California's assessment would appear to be the most appropriate since the male sensitivity was considered and both types of tumours developed in the nasal mucosa, despite that adenocarcinoma was more prominent. Based on the unit risk of $2.7 \times 10^{-6} \bullet(\mu g/m^3)^{-1}$, the risk specific concentrations will be 0.4, 4 and 40 $\mu g/m^3$ at risk levels of 10^{-6}, 10^{-5} and 10^{-4}, respectively.

Acetaldehyde may also act as a **tumour promoter** which promotes the progression of irreversible tumourigenic processes induced by endogenous mutations or by other exogenous initiators (e.g. benzo[a]pyrene) and is regarded as an epigenetic phenomenon. It may act through its specific inhibitory action on the DNA repairing enzyme, O^6-methylguanine transferase, by binding directly to this enzyme or indirectly by depleting the cellular thiol (mainly reduced glutathione) compounds (Espina *et. al*., l988; Grafström *et. al*., 1994). Acetaldehyde also promotes cross-linked envelope formation, a late event in squamous differentiation of epithelial cells (Saladino et. al., 1988; Grafström et. al., 1994). Acetaldehyde-induced DNA-protein cross-links has been suggested to be the cellular mechanism for the carcinogenic activity of this compound. However, it should be noted that studies using human bronchial epithelial cell or human lymphoma cell cultures indicate that DNA-protein cross-links usually occur at cytotoxic concentrations, e.g. >10 mM (Lam *et. al*., 1986; Saladino *et. al*., 1988; Grafström *et. al*., 1994; Costa *et. al.* 1997). These *in vitro* studies indicate that a threshold may exist for these possible tumourigenic events induced by acetaldehyde. In addition, DNA-protein cross-link formation in the respiratory and olfactory mucosa of male rats following inhalation exposure to acetaldehyde has also been reported (Lam *et. al.*, 1986). Acetaldehyde-induced DNA-protein cross-links in the respiratory mucosa following a single inhalation exposure for 6 hours, observed in this *in vivo* study, occurred in a non-linear fashion and the increase was significant only at concentrations equal to or above 1000 ppm (1800 mg/m^3). This indicates that a threshold may exist for this cytogenetic event to

develop. Furthermore, in the olfactory mucosa, significant DNA-protein cross-links formation was observed only in animals exposed repeatedly to 1000 ppm or1800 mg/m^3 of acetaldehyde 5 days (6 hours/day). Lam *et. al.* (1986) suggested that this enhanced DNA-protein cross-link formation in the olfactory mucosa may result from recurrent tissue damage and repair associated with the cytotoxic effect of repeated acetaldehyde exposure.

It is apparent that in rats and hamsters, the formation of squamous cell carcinoma and adenocarcinoma is always accompanied by cytotoxic tissue damages to the upper respiratory tract, such as rhinitis and thickening of the olfactory submucosa, inflammation, keratinization, hyperplasia and/or metaplasia at doses as low as 750 ppm (1350 mg/m^3) to 3000 ppm (5400 mg/m^3). If the nasal tissue damage (e.g. hyperplasia or metaplasia) is not severe enough (at lower doses), regression or regeneration of affected tissues may occur; whereas at higher doses, irreversible progression of hyperplasia and metaplasia into neoplasia will occur (Feron *et. al.,* 1982; Woutersen & Feron, 1987). It is apparent from these whole animal studies that a no-observed-effect dose (threshold dose) for tumour formation may exist. A NOAEL of 150 ppm (270 mg/m^3) based on nasal tissue damage was observed in rats (Appelman *et. al.,*1986). If tumour development is associated with the cytotoxicity of acetaldehyde, an air quality standard based on this end point will also be protective of carcinogenesis.

At present, no conclusion can be drawn from all these animal studies for a definitive mechanism for acetaldehyde carcinogenicity. If acetaldehyde does induce nasal carcinogenic formation by a mutagenic mechanism, the environmental concentration contributed by anthropogenic sources should be kept to a minimum and the risk of exposure is usually estimated using the linearized multi-stage method (a default of the U.S.EPA approach for carcinogen risk assessment). On the other hand, if acetaldehyde-induced tumour development is an epigenetic process, then the risk calculated by the linearized multi-stage method will be overestimates at low environmental concentrations. A threshold concentration (dose) can be anticipated if acetaldehyde is a co-carcinogen or a tumour promoter.

When assessing the acetaldehyde-induced tumour risk in humans, other factors should also be considered, for example: nasal tumour is not common in humans; the human nasal tissue may not be as sensitive as those of the rats and hamsters; the breathing pattern may not be similar between species, e.g. rats are obligatory nose breathers whereas humans breathe through the nose and mouth and therefore the site of contact may be different (Woutersen *et. al.,* 1986; U.S.EPA, 1989); the detoxification ability (mucociliatory removal and metabolic degradation by aldehyde dehydrogenases) may be different (Casanova-Schmitz *et. al*., 1984; U.S.EPA, 1989; Morris, 1997).

3.3.3 Adverse effects of similar aldehydes

In view of the limited research on the biochemical action of acetaldehyde toxicity, studying the structural activity relationship with chemically similar compounds may shed some light into the possible mechanism of action for this compound and may offer support in regulatory decision

making. Among the aldehydes, formaldehyde is considered to be the most appropriate candidate because of its chemical properties, toxicity and possible mode of action in animal studies (Morris, *et. al.,* 1996)[1]. (See also **Appendix 7.8** for more information on these two aldehydes)

Chemically, both acetaldehyde and formaldehyde are electrophilic compounds. Both compounds can react with the amino groups of nucleic acids and the sulfhydro groups of protein. These two compounds have been shown to have the following effects in human cultured cells or animal nasal mucosa preparations: formation of cross-linked envelopes, levels of cytosolic calcium, DNA-protein cross-links, DNA strand breaks and on the DNA repair enzyme (i.e. O^6-methylguanine transferase), colony-forming efficiency and clonal growth rates in cell cultures (Saladino *et. al.,* 1985; Lam *et. al.,* 1986*;* Dellarco, 1988; Grafström, 1990; Grafström *et. al.,*1994). The genotoxic properties of these two compounds are similar but different in the "genotoxicity ranking" in that formaldehyde ranks higher than acetaldehyde (see Morris *et. al.,* 1996).

Both acetaldehyde and formaldehyde exhibit contact-site specific toxicity and the toxicity profiles for these two compounds are remarkably similar. In animals, vapour of either compound induces damages to the upper respiratory tract, e.g. short-term inhalation exposure caused inflammation and degeneration of the nasal mucosa and long-term exposure promoted formation of nasal squamous cell carcinoma and adenocarcinoma whereas other organs were not appreciably affected (Woutersen *et. al.,* 1982; Woutersen *et. al.,* 1987; Grafström, 1990; Grafström *et. al.,*1994).

Morris *et. al.* (1996) compared the relative potency of toxic effects for these two compounds using nasal damage, tumour rate and DNA-adduct formation as indicators and the findings are summarized in Table 2. Working on the basis of cyclic flow conditions and estimates of deposition efficiency for acetaldehyde and formaldehyde in the nasal cavity, the total delivered dosage rate for these two compounds could be calculated and employed in the dosimetry study. Using total carcinoma incidence rates (% of squamous cell carcinoma plus % of adenocarcinoma), assuming total tumour incidence follows a linear fashion, an estimate of a 50% "toxic dose" can be obtained for acetaldehyde (2.9 mg/cm^2/day); formaldehyde at 0.21 mg/cm^2/day induced a 47% total tumour incidence. The relative potency for

[1] Additional references for this Section for the structural activity relationship between acetaldehyde and formaldehyde can be found in Morris *et. al.,*1996.

Table 2. Comparative Dosimetry and Nasal Toxicity of Acetaldehyde and Formaldehyde [a]

	Acetaldehyde				Formaldehyde		
Dosimetry Concentration (ppm)	400	750	1000	1500	3	5.6	14.3
Delivered dose ($mg/cm^2/day$)	1.2	2.2	2.9	4.4	0.043	0.084	0.21
Responses Chronic [b] Squamous cell carcinoma	---	2 %	---	19 %	---	1 %	44 %
Adenocarcinoma	---	31 %	---	58 %	---	3 %	2 %
Total Tumour	---	33 %	---	77 %	---	4 %	46 %
Subchronic [c] LOAEL ($mg/cm^2/day$)	1.2				0.043		
DNA-protein cross-links [d] (% IF DNA in respiratory mucosa)			4 %	—	---	5 %	10 %

Notes:

a) Table has been modified from Morris *et. al.*(1996). See also Morris *et. al.*(1996) for relevant references.

b) Tumour incidence yield was obtained from male rats. The total reflects the sum of the squamous cell carcinoma and the adenocarcinoma incidence as these represent two types which are significantly increased in a concentration dependent manner by aldehyde exposure.

c) Tissue damage is based on subchronic toxicity data. For formaldehyde, 13-week exposure (6 hour/day, 5 days/week) to 3 ppm produces epithelial hyperplasia in the anterior part of the nose, whereas exposure to 1 ppm is without effect. For acetaldehyde, olfactory degeneration was observed in rats exposed to 400 or greater ppm for 4 weeks (6 hour/day, 5 days/week). No NOAEL was observed in the original study. The 400 ppm was estimated to be a LOAEL on the basis of the description of the damage as "slight".

d) IF DNA (interfacial DNA content) is an indirect measure of DNA-protein cross-link formation.

acetaldehyde/formaldehyde can be projected to be 14 (14-fold less potent for acetaldehyde at 2.9 mg/cm^2/day as compared with formaldehyde at 0.21 mg/cm^2/day).

Based on the LOAEL/NOAEL for nasal cytotoxicity induced by subchronic exposure to acetaldehyde or to formaldehyde, the relative potency for acetaldehyde vs formaldehyde can be estimated to be 28-fold less potent for acetaldehyde (acetaldehyde 1.2 mg/cm^2/day *vs* formaldehyde 0.043 mg/cm^2/day).

On the basis of DNA-protein cross-link formation in the respiratory mucosa, acetaldehyde appears to be 34-fold less potent than formaldehyde (at 4-5% formation; acetaldehyde, 2.9 mg/cm^2/day vs formaldehyde, 0.084 mg/cm^2/day).

It is apparent that on a delivered dose basis, acetaldehyde is 14- to 34-fold less potent than formaldehyde to induce carcinogenic and noncarcinogenic damages to nasal tissues of animals. Similar phenomenon is observed in tissue preparations or cultured cells that acetaldehyde is less potent than formaldehyde to elicit cellular events, such as clonal cell growth, cross-linked envelope, DNA-protein cross-links and DNA single strand breaks (Krokan *et. al.,* 1985*;* Saladino *et. al*., 1985; Lam *et. al.,* 1986; Dellarco, 1988; Grafström *et. al*., 1994).

3.4 Recommendation for an Ambient Air Quality Criterion

3.4.1 Available criteria

Agencies such as the U.S.EPA, California and Massachusetts have considered both of the carcinogenicity and the noncarcinogenic effects of acetaldehyde in their agency guidelines (Table 1). However, the rationales underlying their guidelines (such as the selection of data for risk assessments, use of occupational exposure limits and the application of science/policy considerations) may be only appropriate for respective agencies. However, MOE concurs with these agencies that the potential cytotoxic and tumourigenic effects on nasal tissues should both be considered in air quality standard or criteria development.

3.4.2 Consideration based on the carcinogenic effect

It has been postulated that acetaldehyde induces nasal tumour development through non-genetic (epigenetic) mechanisms such as repeated damage-repair of mucosal cells associated with hyperplasia and metaplasia of nasal epithelium, or inhibiting the activity of the DNA-repair enzyme, or through some unknown tumour promotion mechanisms. Thus, it is likely that a threshold concentration for these epigenetic tumour-promoting activity of acetaldehyde may exist. This notion can be supported by the observation that nasal squamous cell carcinoma and adenocarcinoma occur wherever there is severe damage to the nasal mucosal tissue, particularly at high exposure concentrations, e.g. > 1000 ppm (or >1800 mg/m^3).

Until quantitative data is available to obtain a threshold for acetaldehyde carcinogenicity, agencies such as the U.S.EPA, California, Massachusetts adopted a default assumption that acetaldehyde-induced changes in the genetic material of nasal cells predispose to tumour formation. Using the linearized multi-stage model, the 95 % upper bound unit risk estimates agree well among these three agencies (Table 1). This method is likely an overestimate of carcinogenic risk if a threshold dose does exist in acetaldehyde-induced tumour development.

Based on the evaluation of carcinogenic information from all aspects including the association of cytotoxic effect in acetaldehyde carcinogenesis, the likelihood of a promoter (threshold) mechanism, the lack of a common occurrence of nasal tumour in humans, the observed lower carcinogenic potency as compared with formaldehyde, the Ministry considers that acetaldehyde is not likely to induce tumour development at exposure concentrations which do not cause cytotoxic effects.

3.4.3 Consideration based on the noncarcinogenic effect

The study of Appelman *et. al.* (1986) was considered a principal study for the noncarcinogenicity-based criteria developed by various agencies. The pathological lesion of the rat nasal tissues following acetaldehyde treatment in this short-duration (4-week) study was also observed in rats and hamsters in long-term studies (Feron *et. al*, 1982; Woutersen *et. al*., 1986; Woutersen and Feron, 1987). Thus, the NOAEL of 150 ppm (273 mg/m^3) in this short-duration study was also considered a valid observation in chronic exposure investigations. The U.S.EPA converted this NOAEL of 273 mg/m^3 for rats to a human-equivalent $NOAEL_{HEC}$ and applied an uncertainty factor of 1000 to obtain a final RfC of 0.009 mg/m^3 (9 $\mu g/m^3$). It is noted that the RfC of the U.S.EPA is described as an estimate, with an uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effects during a lifetime of exposure. California adopted the RfC from the U.S.EPA as its chronic exposure level (REL). The WHO (through IPCS) employed the same NOAEL of 273 mg/m^3 from Appelman *et. al.*, (1986) to develop its tolerable concentration of 0.3 mg/m^3 (300 $\mu g/m^3$). The WHO did not consider an extrathoracic respiratory conversion.

The incorporation of an extrathoracic respiratory conversion from rats to humans for acetaldehyde may lead to an overestimate in risk. Firstly, inhaled acetaldehyde demonstrates a high degree of site-specific (port of entry) action, damages mostly occur in the nasal cavity. Secondly, retention of inspired acetaldehyde is not related to breathing rate or tidal volume. Results from studies on acetaldehyde exposure by inhalation (0.4 - 0.6 µg/mL or 400 - 600 mg/m^3) with humans and dogs indicated that in humans the percent retention (the percent difference between the amount of inhaled acetaldehyde in a given exposure period and the amount exhaled) of acetaldehyde was inversely proportional to the respiratory rate. The percent uptake (the difference between the amount inhaled and the amount retained) declined with increasing acetaldehyde concentrations. There was no difference in acetaldehyde retention between nose or

mouth breathing in humans. Total retention was independent of the tidal volume but the uptake (the difference between the amount in the system before and after the exposure period) was dependent on the frequency and duration of respiration. In mongel dogs, the total respiratory tract retention value for acetaldehyde was similar to that of humans and inversely related to the respiratory rate. The uptake of acetaldehyde in the dogs was greater in the upper than in the lower tract and independent of tidal volume and inhaled concentrations (see ref. California EPA, 1993; U.S.EPA, 1997; WHO, 1995). Thirdly, uptake of acetaldehyde is not consistent with inspired concentrations among animal species. The phenomenon of decreased nasal acetaldehyde uptake efficiencies at high (1000 ppm) compared with low (1 and 10 ppm) inspired concentrations and also at increasing flow rate among rodents was documented (Morris, 1997). It was suggested that some saturation process may exist. Morris (1997) also reported that exposure concentration and delivered dose relationship for the nose of the rodents were very different at high exposure concentrations (such as those used in toxicity testing). The delivered dose and the inspired concentrations do not follow a linear relationship in the various rodents tested. In addition, the metabolic capacity (the sum of the V_{max} for the high and low affinity isoenzymes) and the type of isoenzymes in the nasal tissue were different among rodents. Diminished nasal uptake may allow higher concentrations to reach the pulmonary area for the toxic effect of acetaldehyde. Thus, the extrapolation of high inhalation concentration data from rodent studies to assess effects at low concentrations should be exercised with caution.

3.4.4 Derivation of an Air Quality Criterion for Acetaldehyde for Ontario

In light of consistent observations concerning the relationship between tissue damage and the development of tumours, the Ministry considers tissue damage to be a precondition for tumour formation for inhalation exposure to acetaldehyde. In this regard, the NOAEL of 150 ppm (270 mg/m^3), as reported by Appelman *et. al*. (1986) is considered the most appropriate basis for developing an Ontario Ambient Air Quality Criterion for acetaldehyde .

In developing an Ambient Air Quality Criterion for acetaldehyde, it is necessary to apply uncertainty factors to the NOAEL to account for the fact that the NOAEL was derived from observations of laboratory animals experimentally exposed to acetaldehyde.

- Exposure scenarios to derive the NOAEL were based on exposure periods of 6 hour/day and 5 days/week reported in (Appelman *et. al*. 1986). To account for continuous exposures, a conversion factor of 0.179 (6hr/24hrs * 5days/7days) is used.

- To account for variability across species, a default uncertainty factor of 10 is often used. The U.S.EPA and the WHO employed such a default factor in developing their reference concentrations for acetaldehyde and the Ministry recommends retaining such a factor because of the deficiency in human nasal or respiratory effect data and the high variability in the uptake and metabolism of acetaldehyde among animal species.

- Experimental observation suggests that male animals may appear to be more sensitive than female animals to the detrimental effect of air-borne acetaldehyde, particularly with reference to the likelihood of tumour development. As there is no data to assess variability among the human population, an factor of 10 is recommended to account for this possibility.

- The U.S.EPA in deriving their RfC and the WHO in deriving a tolerable intake for acetaldehyde, applied a default safety factor of 10 to account for the fact that the NOAEL was derived from subchronic exposures in animals. In reviewing the effects of acetaldehyde, changes or damages to the nasal epithelia following inhalation of acetaldehyde can be observed after 3 days (Cassee *et al*., 1996), 4 weeks (Appelman *et al*. 1986), or 52 weeks (Woutersen *et. al*., 1986; Woutersen and Feron, 1987). In addition, the severity of the damage to nasal tissue is apparently not exposure duration-related, rather, a dose-response relationship is often observed. In fact, the lesions are greatly reduced or disappear if exposure is ceased (Woutersen and Feron, 1987). Based on these observations and the fact that a factor has already been incorporated to extrapolate from intermittent to continuous exposure, the Ministry considers the application of an uncertainty factor to extrapolate from subchronic to chronic exposures to be unnecessary for acetaldehyde.

An air quality criterion of 500 $\mu g/m^3$ is derived by applying an uncertainty factor of 100 (10*10) and an exposure period conversion factor of 0.179 to the NOAEL of 150 ppm (273 mg/m^3) (Appelman *et al*., 1986). Chronic daily exposures to airborne acetaldehyde at or below 500 $\mu g/m^3$ are not likely to be detrimental to the health of the Ontario population. The Ministry therefore recommends that the 24-hour Ambient Air Quality Criterion for acetaldehyde be 500 $\mu g/m^3$.

The relationship between air quality guidelines of different averaging times is based on empirically derived factors which are used to relate short-term maxima concentrations to long-term averages. The factors are selected to ensure that if the short-term limit is met (e.g. half-hour POI limit or 24-hour AAQC), air quality guidelines based on longer-term exposure will not be exceeded. The factor typically used to convert from a 24-hour average to an half-hour maximum is 3 (MOEE 1994c). Depending on the critical end-point being considered other factors may also be employed. For acetaldehyde, observations from animal studies suggest that irritation and tissue damage of the upper respiratory tract can occur after short-term exposures. For this reason, the Ministry recommends that the half-hour point of impingement criterion for acetaldehyde be 500 $\mu g/m^3$ to protect against the possibility of irritancy from short-duration exposure (Table 3).

Table 3: Recommended AAQC and POI Guideline for Acetaldehye		
AAQC	24-Hour Average	500 µg/m^3
POI Guideline	Half-hour Average	500 µg/m^3

While an the recommended air quality standards for acetaldehyde are based on the prevention of adverse health effects in the human population, the potential effects of acetaldehyde on other terrestrial biota including plants, soil microbes and herbivores was also examined. Limited available toxicity data based on animal study data and additional modelling information indicate that exposure to acetaldehyde at or below the proposed AAQC is also not likely to be detrimental to other biota in Ontario.

4.0 Status of Stakeholder Consultations

In January 1997, the Ministry initiated limited stakeholder consultation on the initial suite of 14 proposed air standards developed under the Standards Plan (MOEE, 1996). During the course of these consultations, written comments were received from several stakeholders expressing concern over thescientific basis of the standard proposed. The stakeholders pointed out that both acetaldehyde and formaldehyde were structurally similar compounds with similar toxicological profiles. However, acetaldehyde was toxicologically less active than formaldehyde. Supporting literature were provided by the stakeholders to the Ministry for review. Based on a review of the originally proposed criterion and a review of the literature, the Ministry has undertaken a more in-depth scientific evaluation for acetaldehyde which has led to the revised recommendation.

5.0 Recommendations

The Ministry of the Environment has reviewed and considered air quality guidelines and standards used by leading agencies world-wide. Of the criteria reviewed from other agencies none were considered adequate. However, the Ministry has evaluated and accepts the scientific studies which support the development of the Reference Concentration established by the United States Environmental Protection Agency and the 24-hour average chronic Reference Exposure Level established by the State of California. After reviewing additional toxicological information and the similarity of the mode of action and differences in activities of a related compound, formaldehyde, the Ministry considers that the uncertainty factors used to derive exposure limits by the United States Environmental Protection Agency and the State of California are overly conservative.

Based on evaluations of additional toxicological information; similarity of the mode of action and differences in toxicological activities between acetaldehyde and formaldehyde; the levels of

acetaldehyde measured in Ontario; modelled ground level concentrations from recent applications for Certificates of Approval; the Ministry is proposing to establish:

- a 24-hour average Ambient Air Quality Criterion for acetaldehyde 500 µg/m^3 (micrograms per cubic metre of air).

- an interim Point of impingement guideline of 500 µg/m^3 (half-hour average concentration). The point of impingement guideline is based on the possibility of the irritant property of acetaldehyde due to short-term exposures and will be used to review and assess applications for Certificates of Approval involving emissions of acetaldehyde from new or modified sources.

Acetaldehyde has been included in the second Priority Substances List to be assessed for its toxicity under the *Canadian Environmental Protection Act* (CEPA). The Ministry will re-evaluate the proposed air quality standards for acetaldehyde at the time the assessment under CEPA is completed.

6.0 References

ACGIH, 1986. Documentation Of The Threshold Limit Values for Substances in Workroom Air (5th ed.). American Conference of Governmental Industrial Hygienists Inc., Cincinnati, OH.

AIHA, 1989. Odour Threshold for chemicals with Established Occupational Health Standards. American Industrial Hygiene Association, Akron, Ohio, U.S.A..

ACGIH, 1991. Documentation Of The Threshold Limit Values for Substances in Workroom Air (6th ed.). American Conference of Governmental Industrial Hygienists Inc., Cincinnati, OH.

Appelman, L.M., R.A. Woutersen and V.J. Feron, 1982. Inhalation toxicity of acetaldehyde in rats: I. Acute and subacute studies. Toxicology, **23**:293-307.

Appelman, L.M., R.A. Woutersen, V.J. Feron, R.N. Hooftman and W.R.F. Notten, 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol., **6(5)**:331-336.

Bell, R.W., R.E. Chapman, B.D. Kruschel and M.J. Spencer, 1994. A comparison of air quality in smoking and non-smoking areas: private homes and bingo halls. Presented at the "Measurement of Toxic and Related Air Pollutants," an AWMA Symposium sponsored by the U.S.EPA in Durham N.C., August, 1994.

CAPCOA, 1993. Air Toxics "Hot Spots" Program. Revised 1992 Risk Assessment Guidelines. Toxics Committee of the California Air Pollution Control Officers Association.

CARB, 1993. Acetaldehyde as a Toxic Air Contaminant. Stationary Source Division, California Environmental Protection Agency Air Resources Board.

Commonwealth of Massachusetts, 1990. The Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits, Volumes I and II. Commonwealth of Massachusetts, Department of Environmental Protection, Boston, MA.

California EPA, 1993. Acetaldehyde as a Toxic Air Contaminant. Part B, Health Assessment. Air Resources Board, California Environmental Protection Agency.

Casanova-Schmitz, M., David, R.M. and Heck, H.D. 1984. Oxidation of Formaldehyde and Acetaldehyde by NAD^+-dependent Dehydrogenases in Rat Nasal Mucosal Homogenates. Biochem. Pharmacol. **33**:1137-1142.

Cassee, F.R., J.P. Groten and V.J. Feron. 1996. Changes in the Nasal Epithelium of Rats Exposed by Inhalation to Mixtures of Formaldehyde, Acetaldehyde and Acrolein. Fund. Appl. Toxicol. **29**:208-218.

Costa, M., A. Zhitkovich, M. Harris, D. Paustenbach and M. Gargas, 1997. DNA-protein cross-links produced by various chemicals in cultured human lymphoma cells. J. Toxicol. Environ. Health **50**:433-449.

Dellarco, V.K., 1988. A mutagenic assessment of acetaldehyde. Mutation Res. **195**:1-20.

Dulout, F.N. and C.C. Furnus, 1988. Acetaldehyde-induced aneuploidy in cultured Chinese hamster cells. Mutagenesis, **3(3)**:207-211.

Environment Canada, 1991. Detroit Incinerator Monitor Program, Data Report #5. Environment Canada, Ottawa, Canada.

Espina, N., V. Lima, C.S. Lieber & A. J. Garro, 1988. *In vitro* and *in vivo* inhibitory effect of ethanol and acetaldehyde on O^6-methylguanine transferase. Carcinogenesis **9(5)**:761-766.

Feron, V.J., 1979. Effects of Exposure to Acetaldehyde in Syrian Hamsters Simultaneously Treated with Benzo(a)pyrene or Diethylnitrosamine. Prog. Exp. Tumor Res., **24**:162-176.

Feron, V.J., A. Kruysse and R.A. Woutersen, 1982. Respiratory tract tumours in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine. Eur. J. Cancer Clin. Oncol., **18**:13-31.

Grafström, R.C., 1990. In vitro studies of aldehyde effects related to human respiratory carcinogenesis. Mutation Res. **238**:175-184.

Grafström, R.C., J.M. Dypbuk, K. Sundqvist, L. Atzori, I. Nelson, R.D. Curren & C.C. Harris, 1994. Pathological effects of acetaldehyde in cultured human epithelial cells and fibroblasts. Carcinogenesis, **15(5)**:985-990.

Harris, C.C, 1991. Chemical and Physical Carcinogenesis: Advances and Perspectives for the 1990s. Cancer Res. [Suppl.] **51**:5023s-5044s.

IARC, 1985. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Volume 36. Allyl Compounds, Aldehydes, Epoxides and Peroxides. International Agency for Research on Cancer, Lyon, France.

IARC, 1987. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42. Supplement 6. International Agency for Research on Cancer, Lyon, France. 697+ p.

IARC, 1995. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Wood dust and formaldehyde. Volume 62. International Agency for Research on Cancer, Lyon, France. 242+ p.

Kruysse, A., V.J. Feron and H.P.Til, 1975. Repeated Exposure to Acetaldehyde Vapor: Studies in Syrian Golden Hamsters. Arch. Environ. Health, **30**:449-452.

Lam C.-W., M. Casanova and H.D'A. Heck, 1986. Decreased Extractability of DNA for Proteins in the Rat Nasal Mucosa after Acetaldehyde Exposure. Fund. Appl. Toxicol. **6**:541-550.

Lambert, B. & S-.M. He, 1988. DNA and Chromosome Damage Induced by Acetaldehyde in Human Lymphocytes *in Vitro*. Ann. New York Acad. Sci., **534**:369-376.

McConnell, E.E., 1995. Historical review of the rodent bioassay and future directions. Reg. Toxicol. Pharmacol., **21**:38-43.

MOEE, 1994a. Summary of Point of Impingement Standards, Ambient Air Quality Criteria (AAQCs) and Approvals Screening Levels (ASLs). Standards Development Branch, Ontario Ministry of the Environment and Energy, Toronto, Ontario.

MOEE, 1994b. Windsor Air Quality Study: Health Effects Assessment. Appendices 1-24. Ontario Ministry of the Environment and Energy, Toronto, Ontario.

MOEE, 1996. Three Year Plan for Standards-Setting. Ministry of Environment and Energy, Toronto, Ontario.

Meek, M.E. and R. Gomes, 1997. Personal communications, Health Canada.

Morris, J.B., D.E. Robinson, T.A. Vollmuth, R.P. Brown, B.E. Domeyer, 1996. A parallelogram Approach for Safety evaluation of Ingested Acetaldehyde. Regulatory Tox. Pharmacol. **24**:251-263.

Morris, 1997. Uptake of Acetaldehyde Vapour and Aldehyde Dehydrogenase Levels in the Upper Respiratory Tracts of the Mouse, Rat, Hamster and guinea Pig. Fund. Appl Toxicol. **35**:91-100.

NeR Staff Office, 1992. Netherlands Emission Regulations - Air. Netherlands Emission Regulations Staff Office, Bilthoven, The Netherlands. 81 p. + Appendices.

Netherlands MHSPE, 1994. Environmental Quality Objectives in The Netherlands. A review of environmental quality objectives and their policy framework in The Netherlands. Risk Assessment and Environmental Quality Division, Ministry of Housing, Spatial Planning and the Environment (MHSPE), The Hague, The Netherlands. 465 p.

New York State DEC, 1991. New York State Air Guideline -1. Guidelines for the Control of Toxic Ambient Air Contaminants. Draft. New York State Department of Environmental Conservation (DEC), Albany, N.Y. 20 p. + Appendices.

NPRI, 1993. The National Pollutant Release Inventory, summary report of 1993. Canadian Environmental Protection Act. Environment Canada.

NPRI, 1994. The National Pollutant Release Inventory, summary report and database of 1994. Canadian Environmental Protection Act. Environment Canada.

NPRI, 1995. The National Pollutant Release Inventory, summary report and database of 1995. Canadian Environmental Protection Act. Environment Canada.

Recio, L., Sisk, S., Pluta, L., Bermudez, E., Gross, E.A., Chen, Z., Morgan, K. and Walker, C., 1992. *p53* Mutations in Formaldehyde-induced Nasal Squamous Cell Carcinoma in Rats. Cancer Res., 52:6113-6116.

Saladino, A.J., J.C.Willey, J.F. Lechner, R.C. Grafström, M. LaVeck & C.C. Harris, 1985. Effects of Formaldehyde, Acetaldehyde, Benzoyl Peroxide, and Hydrogen Peroxide on Cultured Normal Bronchial Epithelial Cells. Cancer Res. **45**:2522-2526.

Shepson, P.B., D.R. Hastie, H.I. Schief, M. Polizzi, J.W. Bottenheim, K. Anlauf, G.I. MacKay and D.R. Karecki, 1991. Atmospheric Concentrations and Temporal Variations of C_1-C_3 Carbonyl Compounds at Two Rural Sites in Central Ontario. Atmospheric Environment, **25A**:2001-2015.

Shiohara, E., M. Tsukada, S. Chiba, H. Yamazaki, K. Nishiguchi, R. Miyamoto and S. Nakanishi, 1985. Effect of Chronic Administration of Acetaldehyde by Inhalation on (Na^+-Ka^+)-activated Adenosine Triphosphatase Activity of Rat Brain Membranes. Toxicology, **34**:277-284.

Singh, N.P. and A. Khan, 1995. Acetaldehyde: genotoxicity and cytotoxicity in human lymphocytes. Mutation Res. **337**:9-17.

Steer, P. 1996. Personal communication, MOEE. (Data obtained from T. Dann of Environment Canada.)

U.S.EPA, 1986. Health Assessment Document for Acetaldehyde. Review Draft. Office of Health and Environmental Assessment, United States Environmental Protection agency.

U.S.EPA, 1989. Interim Methods for Development of Inhalation Reference Doses. Office of Health and Environmental Assessment, United States Environmental Protection agency.

U.S.EPA, 1997. Integrated Risk Information System (IRIS) Database. U.S. Environmental Protection Agency, Washington, D.C.

USNRC (U.S. National Research Council), 1981. Health Effects of Some Other Aldehydes. In: Formaldehyde and Other Aldehydes. National Academy Press, Washington, D.C., as cited in ACGIH, 1991.

Victorin, K., 1993. Health effects of urban air pollutants: guideline values and conditions in Sweden. Chemosphere, **27**:1691-1706.

WHO, 1987. Air Quality Guidelines for Europe. WHO Regional Publications, European Series No. 23. World Health Organization, Regional Office for Europe, Copenhagen, Denmark. 426 p.

WHO, 1995. Environmental Health Criteria 167, Acetaldehyde. International Programme on Chemical Safety. World Health Organization, Geneva.

Woutersen, R.A., Appelman, L.M., Feron, V.J. and Van der Heijden, C.A., 1984. Inhalation toxicity of acetaldehyde in rats. II. Carcinogenicity study: interim results after 15 months. Toxicology, **31**:123-133.

Woutersen, R.A., Van der Heijden, C.A. and Appelman, L.M, 1985. Lifespan (27 months) inhalation carcinogenicity study of acetaldehyde in rats. Final report. Report No. V85.145/190172. Civo Institute TNO, The Netherlands. (Unpublished).

Woutersen, R.A., L.M. Appelman, A. Van-Garderen-Hoetmer and V.J. Feron, 1986. Inhalation toxicity of acetaldehyde in rats, III: Carcinogenicity study. Toxicology, **41**:213-232.

Woutersen, R.A. and V.J. Feron, 1987. Inhalation toxicity of acetaldehyde in rats, IV: Progression and regression of nasal lesions after discontinuation of exposure. Toxicology, **47**:295-304.

7.0 Appendix: Agency-Specific Reviews of Air Quality Guidelines

7.1 Agency-Specific Summary: Federal Government of the United States

1. Name of Chemical: Acetaldehyde

2. Agency: U.S. Environmental Protection Agency

3. Guideline Value(s):
No ambient air exposure limits are currently promulgated. There is a reference concentration (RfC) of 9.0 $\mu g/m^3$ for chronic inhalation exposure in the IRIS database (U.S.EPA, 1997). There are also quantitative estimates of carcinogenic risk from inhalation exposure. The inhalation unit risk is $2.2*10^{-6}$ tumours per $\mu g/m^3$ (last revised in 1991). Using a two-stage model extrapolation procedure, this represents an additional risk of 1 in 100,000 for 5 $\mu g/m^3$ lifetime exposure and 1 in 1,000,000 for 0.5 $\mu g/m^3$ lifetime exposure.

4. Application:
IRIS was developed as a source of consistent risk information on chemicals for use in decision-making and regulatory activities. However, values derived and presented in IRIS, in and of themselves, do not represent guidelines or standards. IRIS also contains a summary of current American government regulatory actions under various legislative mandates.

5. Documentation Available:
U.S.EPA, 1997. Integrated Risk Information System (IRIS) Database. U.S. Environmental Protection Agency, Washington, D.C.

Key Reference(s):
Appelman, L.M., R.A. Woutersen and V.J. Feron, 1982. Inhalation toxicity of acetaldehyde in rats, I: Acute and subacute studies. Toxicology, 23:293-297.

Appelman, L.M., R.A. Woutersen, V.J. Feron, R.N. Hooftman and W.R.F. Notten, 1986. Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol., 6(5):331-336.

Feron, V.J., A. Kruysse and R.A. Woutersen, 1982. Respiratory tract tumours in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine. Eur. J. Cancer Clin. Oncol., 18:13-31.

Woutersen, R.A., Appelman, L.M., Feron, V.J. and Van der Heijden, C.A., 1984. Inhalation toxicity of acetaldehyde in rats. II. Carcinogenicity study: interim results after 15 months. Toxicology, **31**:123-133.

Woutersen, R.A., Van der Heijden, C.A. and Appelman, L.M, 1985. Lifespan (27 months) inhalation carcinogenicity study of acetaldehyde in rats. Final report. Report No. V85.145/190172. Civo Institute TNO, The Netherlands. (Unpublished).

6. Peer Review Process and Public Consultation:

Peer-reviewed scientific research data, analyses and evaluations from various sources, including a variety of public and government agencies from around the world and the published scientific literature, were employed in the development of these values. Both the general assessment methodologies and the chemical-specific information found in IRIS undergo extensive scientific and policy reviews, both within the EPA and within other science-based U.S. regulatory agencies. Much of the information that appears in IRIS is based on documents that have been submitted to scientific peer-review and public review.

7. Status of Guideline:

No guideline exists. The risk estimate discussed is for respiratory exposure from air only.

8. Key Risk Assessment Considerations:

The U.S.EPA has calculated an RfC which represents risk from adverse effects other than cancer. It has also calculated a unit risk, based on the carcinogenic potential of acetaldehyde (U.S.EPA, 1997). The U.S.EPA calculated an RfC, using two short-term rat studies conducted by Apeman *et al*. (1982; 1986). From these studies, the U.S.EPA established a concentration-response for observed degeneration of the nasal olfactory epithelium after 4 weeks of exposure. According to the U.S.EPA, these lesions were consistent with pathology seen in chronic studies of longer exposure times and higher exposure levels. (Woutersen *et al*., 1986; Woutersen and Feron, 1987; Kruysse *et al*., 1975). An exposure level of 150 ppm was chosen as the no-observed-adverse-effect level (NOAEL) from the Apeman *et al*. (1986) study, and an exposure level of 400 ppm was chosen as the lowest-observable-adverse-effect level (LOAEL) from the Apeman *et al*. (1982) study.

The no-observed-adverse-effect level of 150 ppm was converted to a human dose in the extrathoracic area by dosimetric conversion. Assuming 25°C and 760 mmHg, the NOAEL from the Apeman *et al*. (1986) was calculated to be 273 mg/m^3. This value was adjusted for the relative breathing rates between rats and humans over the study period and for the relative surface areas of the extrathoracic region. The human equivalent NOAEL was calculated to be 8.7 mg/m^3based on the following:

the NOAEL was adjusted to a $NOAEL_{adj}$ for continuous exposure, $NOAEL_{adj}$ = 270 mg/m^3 x 6 hours/day x 5 days/7 days = 48.21 mg/m^3; this $NOAEL_{adj}$ was further converted to a NOAEL for human equivalent concentration based on the gas:respiratory extrathoracic effect from rats to humans by multiplying by a factor of 0.18, i.e. $NOAEL_{(HEC)}$ = 48.21 mg/m^3 x 0.18 = 8.7 mg/m^3).

An uncertainty factor of 10 was applied to account for sensitive human populations. A further factor of 10 was applied for both uncertainty in the interspecies extrapolation using dosimetric adjustments and to account for the incompleteness of the data base. An additional factor of 10

was applied to account for subchronic to chronic extrapolation. The RfC was reported to be 0.009 mg/m^3.

The U.S.EPA has classified acetaldehyde as a probable human carcinogen (Classification B2), based on increased incidence of nasal tumours in male and female rats (Woutersen *et. al.*,1984; Woutersen *et. al.,* 1985) and laryngeal tumours in male and female hamsters after inhalation exposure (Feron *et al*., 1982). Using a linearized, multistage-variable exposure input model, the inhalation unit risk was calculated to be $2.2*10^{-6}$ tumours per $\mu g/m^3$.

9. Key Risk Management Considerations:
None, since no guideline for ambient air exists.

10. Multimedia Considerations of Guidelines:
None are reported.

11. Other Relevant Factors:
According to the U.S.EPA (1995), acetaldehyde is similar in structure to formaldehyde, which also produces nasal tumours in animals exposed by inhalation.

Acetaldehyde has been shown by several laboratories to induce sister chromatid exchange (SCE) in cultured mammalian cells (Obe and Ristow, 1977; Obe and Beer, 1979; deRaat *et al*., 1983; Bohlke *et al*., 1983; Ristow and Obe, 1978; Jansson, 1982; Norrpa *et al*., 1985), some of which may persist for several cell generations (He and Lambert, 1985). The induction of SCE by acetaldehyde has also been detected in bone marrow cells of mice and hamsters *in vivo* (Obe *et al*., 1979; Korte and Obe, 1981). Acetaldehyde caused chromosomal aberrations in mammalian cell culture (Bird *et al*., 1981; Bohlke *et al*., 1983) and plants (Rieger and Michaelis, 1960), but not in Drosophila (Woodruff *et al*., 1985). Chromosome gaps and breaks were found in rat embryos after a single intra-amniotic injection on day 13 of gestation (Barilyak and Kozachuk, 1983). Acetaldehyde produced sex-linked, recessive, lethal gene mutations after injection in Drosophila (Woodruff *et al*., 1985), but has been negative in testing in Salmonella (Commoner, 1976; Laumbach *et al*., 1976; Pool and Wiesler, 1981; Marnett *et al*., 1985; Mortelmans *et al*., 1986). Acetaldehyde has been shown to produce crosslinks between protein and DNA in the nasal respiratory mucosa (Lam *et al*., 1986) (all references in above paragraph as cited in U.S.EPA (1997)).

7.2 Agency-Specific Summary: State of California

1. Name of Chemical: Acetaldehyde

2. Agency: State of California (Office of Environmental Health Hazard).

3. Guideline Value(s):
The Reference Exposure Level of 9.0 $\mu g/m^3$ is to be used for assessing chronic effects other than cancer risk. The State of California states that the unit risk of $2.7x10^{-6}$ (0.0000027) tumours/($\mu g/m^3$) is to be used for evaluation of cancer risks. For $1x10^{-5}$ or $1x10^{-6}$ additional cancer risk levels, this corresponds to air concentrations of 4.0 $\mu g/m^3$ and 0.4 $\mu g/m^3$, respectively, for lifetime exposures.

4. Application:
"The intent of the Committee in developing the guideline was to provide risk assessment procedures for use in the Air Toxics 'Hot Spots' Program." (CAPCOA, 1993). This program is based on a California State law: the Air Toxics 'Hot Spots' Information and Assessment Act of 1987 (Health and Safety Code Section 44360 *et seq*.). The act specifies how local Air Pollution Control Districts determine which facilities in their areas will prepare health risk assessments, how such health risk assessments should be prepared and how the results are to be prioritized. These guidelines were prepared to provide consistent risk assessment methods and report presentation to enable: 1) comparisons between facilities, 2) expeditious review of risk assessments by reviewing agencies, and 3) minimal revisions and resubmittals of risk assessments. The various health-based exposure levels developed and used in this program should not be employed outside the program framework. That is to say, the State of California does not consider them to be general, independent, legally enforceable air quality guidelines or limit values at this time.

5. Documentation Available:
CAPCOA, 1993. CAPCOA Air Toxics "Hot Spots" Program. Revised 1992 Risk Assessment Guidelines. Toxics Committee of the California Air Pollution Control Officers Association (CAPCOA).

Key Reference(s):
CARB, 1993. Acetaldehyde as a Toxic Air Contaminant. Stationary Source Division, California Environmental Protection Agency Air Resources Board.

Woutersen, R.A., L.M. Apeman, A. Van-Garderen-Hoetmer and V.J. Feron, 1986. Inhalation toxicity of acetaldehyde in rats, III: Carcinogenicity study. Toxicology, 41:213-232.

6. Peer-Review Process and Public Consultation:
Cancer potency slope factors and acute and chronic reference levels were prepared by the California Office of Environmental Health Hazard Assessment (OEHHA), and these as well as the exposure and health assessments have undergone public review and comment prior to finalization. Peer-reviewed scientific research data were employed in the development of these values. Under the CAPCOA risk assessment process, each assessment is site-specific, and public notice to all exposed individuals is required when the screening process determines that a significant health risk is associated with emissions from a facility. Public input was obtained in identifying and ranking areas and facilities for risk assessment screening, and, according to the documentation, additional input is expected as the process moves forward.

7. Status of Guideline:
Current, but updates are possible, with new California risk assessment guidelines being considered in the California Senate.

8. Key Risk Assessment Considerations:
California agrees with the U.S.EPA's RfC of 0.009 mg/m^3 as its Reference Exposure Level (chronic).

California recognizes the IARC assessment that there was sufficient evidence of carcinogenicity in animals and that the evidence in humans was inadequate. They also noted the U.S.EPA classification of acetaldehyde carcinogenicity as 2B, meaning a probable human carcinogen, "based on increased incidence of nasal tumours in male and female rats and laryngeal tumours in male and female hamsters after inhalation."

California fitted a linearized multistage model (GLOBAL 86) to the male and female rat nasal tumour data reported by Woutersen *et al*. (1986). Animals in the highest concentration group (3000 ppm or 5460 mg/m^3) were not considered for tumour risk estimates because of severe growth retardation and early mortality. Total tumour incidence (squamous cell carcinoma and adenocarcinoma) at 0, 750, 1500 ppm (0, 1365, 2730 mg/m^3) for male rats was 1/49, 17/52, 41/53 whereas for female rats was 0/50, 6/48, 34/53, respectively. Using three plausible interspecies scaling factors (no difference in dose conversion between and humans; conversion based on metabolic rate proportional to body surface area; conversion based on contact site scaling), the range of unit risks for male and female rats ranged from $0.54 \times 10^{-6} \cdot (\mu g/m^3)^{-1}$ to $15.0 \times 10^{-6} \cdot (\mu g/m^3)^{-1}$. California reports that the inhalation unit risk estimate of $2.7 \times 10^{-6} \cdot (\mu g/m^3)^{-1}$ as the "best value". This agency considers that the male rats are more sensitive than the female rats. The interspecies dose conversion factor between rats and humans is based on surface area correction (1.5 for a 400 g male rat and 1.6 for a 250 g female rat).

9. Key Risk Management Considerations:
The exposure guidelines were prepared for both non-cancer and cancer-based endpoints. The cancer-based value is to be used in a facility-based screening risk assessment to determine the maximum offsite cancer risk for the exposed human population. The process is not readily

comparable to the air quality guideline approach to non-carcinogens. The non-cancer guidelines are based on the most sensitive adverse health effect reported in the scientific literature and are designed to protect the most sensitive individuals in the population.

There are options for addressing the possible economic impacts of controlling acetaldehyde emissions. It appears that the options are under local control and are based on local risk and socioeconomic analyses, as well as public workshops and hearings. The enforcement mechanism is via operating permits. Thus, the process is primarily directed towards site-specific evaluations and development of further regulatory tools, rather than being enforceable levels in and of themselves.

10. Multimedia Considerations of Guidelines:
In the exposure modelling process, non-inhalation pathways should be considered for a number of substances (specified in Table III-5 in CAPCOA, 1993). Acetaldehyde is not one of the substances requiring non-inhalation modelling.

11. Other Relevant Factors:
California considers acetaldehyde to be mutagenic and a non-threshold carcinogen.

7.3 Agency-Specific Summary: World Health Organization

1. Name of Chemical: Acetaldehyde

2. Agency: World Health Organization

3. Guideline Value(s):
None

4. Application:
None

5. Documentation Available:
WHO, 1987. Air Quality Guidelines for Europe. WHO Regional Publications, European Series No. 23. World Health Organization, Regional Office for Europe, Copenhagen, Denmark. 426p.

Key Reference(s):
None

6. Peer Review Process and Public Consultation:
None

7. Status of Guideline:
No information

8. Key Risk Assessment Considerations:
No information

9. Key Risk Management Considerations:
No information

10. Multimedia Considerations of Guidelines:
No information

11. Other Relevant Factors:
No information

7.4 Agency-Specific Summary: The Netherlands

1. Name of Chemical: Acetaldehyde

2. Agency: Netherlands Ministry of Housing, Spatial Planning and the Environment

3. Guideline Value(s):
None

4. Application:

5. Documentation Available:
Netherlands MHSPE, 1994. Environmental Quality Objectives in The Netherlands. A review of environmental quality objectives and their policy framework in The Netherlands. Risk Assessment and Environmental Quality Division, Ministry of Housing, Spatial Planning and the Environment (MHSPE), The Hague, The Netherlands. 465 p.

NeR Staff Office, 1992. Netherlands Emission Regulations - Air. Netherlands Emission Regulations Staff Office, Bilthoven, The Netherlands. 81 p. + Appendices.

6. Peer Review Process and Public Consultation:
No specific information on this issue was presented in the available English language documentation.

7. Status of Guideline:
Current

8. Key Risk Assessment Considerations:
None

9. Key Risk Management Considerations:
None

10. Multimedia Considerations of Guidelines:
None

11. Other Relevant Factors:
No information

7.5 Agency-Specific Summary: Swedish Institute of Environmental Medicine

1. Name of Chemical: Acetaldehyde

2. Agency:
According to Dr. K. Victorin of the Swedish Institute of Environmental Medicine (personal communication), no official Swedish air quality guidelines have been promulgated by the Swedish Environmental Protection Agency.

3. Guideline Value(s):
None

4. Application:
No information

5. Documentation Available:
Victorin, K., 1993. Health effects of urban air pollutants: guideline values and conditions in Sweden. Chemosphere, 27:1691-1706.

Although documentation in Swedish has been prepared, no English language version is available.

6. Peer Review Process and Public Consultation:
No information

7. Status of Guideline:
No information

8. Key Risk Assessment Considerations:
No information

9. Key Risk Management Considerations:
No information

10. Multimedia Considerations of Guidelines:
No information

11. Other Relevant Factors:
No information

7.6 Agency-Specific Summary: New York State

1. Name of Chemical: Acetaldehyde

2. Agency: New York State

3. Guideline Value(s):
The recommended 1-hour average is 43,000 µg/m^3. The recommended annual average is 430 µg/m^3.

4. Application:
". . . they are primarily intended for use in conjunction with the permitting authority and regulatory concerns found in 6NYCRR Parts 200, 201, 212 and 257." (p. 1, NYDEC, 1991). These regulations refer specifically to construction and operation (Certificate to Operate) permits for any sources of air contamination. Rather than being employed as legally enforceable ambient air quality standards, the guidelines are to be employed to aid in the regulatory decision-making process. This process includes the classification of chemicals into groups of high, moderate and low toxicity. The regulatory screening process considers the toxicity classification and the emission rate potential from a facility. An air emission dispersion model is also specified in the process to guide regulators in their assessment of chemical emissions from sources of interest. Both long-term and short-term effects are considered.

5. Documentation Available:
New York State DEC, 1991. New York State Air Guideline -1. Guidelines for the Control of Toxic Ambient Air Contaminants. Draft. New York State Department of Environmental Conservation (DEC), Albany, N.Y. 20 p. + Appendices.

Key reference(s):
ACGIH, 1991. Documentation Of The Threshold Limit Values for Substances in Workroom Air (6th ed.). American Conference of Governmental Industrial Hygienists Inc., Cincinnati, OH.

6. Peer Review Process and Public Consultation:
The scientific documents prepared by New York State employed peer-reviewed data and models, as well as the professional judgments of its scientific staff. There are opportunities for public comment on guidelines and the guideline development process, but specific information on the process for acetaldehyde was not presented in the available documentation.

7. Status of Guideline:
Current

8. Key Risk Assessment Considerations:
New York State (1991) has classified the toxicity of acetaldehyde as moderate. Compounds given the designation of moderate are animal oncogens, developmental and reproductive toxicants,

genotoxic chemicals and other chemicals posing a health hazard to humans. For compounds in this classification, the short-term guideline was developed by dividing a chosen occupational standard by 4.2. The long-term guideline was developed by dividing a chosen occupational standard by 420. In the case of acetaldehyde, New York used the occupational standard of 180 mg/m^3 (ACGIH, 1991).

9. Key Risk Management Considerations:
A specific computer model and guidance manual are provided for use of the guidelines in impact screening analyses as employed in the permitting process. The latest version of Appendix B of the New York State Air Guide -1 is dated April 4, 1994.

10. Multimedia Considerations of Guidelines:
Considers human airborne exposure only

11. Other Relevant Factors:
No information

7.7 Agency-Specific Summary: State of Massachusetts

1. Name of Chemical: Acetaldehyde

2. Agency: Commonwealth of Massachusetts

3. Guideline Value(s):
A 24-hour ceiling limit is 4.89 $\mu g/m^3$, based on the threshold effects exposure limit. The allowable ambient limit (AAL) is 0.44 $\mu g/m^3$ for an annual (1 year) averaging time and is based on consideration of carcinogenic effects and a 10^{-6} risk level.

4. Application:
". . . the Division of Air Quality Control, which is responsible for implementing the Department's air programs, plans to employ the AALs in the permitting, compliance, and enforcement components of the Commonwealth's air program in general, and the air toxics program in particular." (Commonwealth of Massachusetts, 1990, Volume 1, pg. ix). The primary goal is to "protect the public health and welfare from any air contaminant causing known or potentially injurious effects." The ambient air levels developed in this process should not be considered legally enforceable air quality standards, since they deal only with health-related matters and contain no consideration of technological, economic or enforcement concerns. Rather, they should be employed as guidelines in the development of subsequent regulatory action which does contain a broad consideration of all relevant concerns.

5. Documentation Available:
Commonwealth of Massachusetts, 1990. The Chemical Health Effects Assessment Methodology and the Method to Derive Allowable Ambient Limits, Volumes I and II. Commonwealth of Massachusetts, Department of Environmental Protection, Boston, MA.

Key Reference(s):
ACGIH, 1986. Documentation Of The Threshold Limit Values for Substances in Workroom Air (5th ed.). American Conference of Governmental Industrial Hygienists Inc., Cincinnati, OH.

Woutersen, R.A., L.M. Appelman, A.Van-Garderen-Hoetmer and V.J. Feron, 1986. Inhalation toxicity of acetaldehyde in rats, III: Carcinogenicity study. Toxicology, 41:213-232.

6. Peer Review Process and Public Consultation:
Peer-reviewed scientific research data, analyses and evaluations from various sources, including a variety of public and government agencies from around the world and the published scientific literature, were employed in the development of these values. Specifically, evidence from the International Agency for Research on Cancer (IARC), the American National Toxicology Program (NTP) and the U.S.EPA was employed. As guidelines, the process used and values generated are not subject to the extensive review and consultation that air quality standards would be subjected to, but external peer reviews were carried out, and public input was solicited through

at least two public meetings on the Massachusetts methodology and guideline document (D. Manganaro, Massachusetts Department of Environmental Protection, pers. comm.).

7. Status of Guideline:
Current. Although guideline values are periodically updated, revisions to the current value for acetaldehyde are not under consideration (D. Manganaro, Massachusetts Department of Environmental Protection, pers. comm.).

8. Key Risk Assessment Considerations:
The State of Massachusetts has a method for establishing a limit that assumes the compound has a threshold for adverse effects. In the case of acetaldehyde, the 1986 ACGIH occupational limit, reported to be 179.8 mg/m^3 (ACGIH, 1986), was divided by several factors that attempt to extrapolate from a worker health-based limit to a public limit that protects children and other sensitive individuals. The uncertainty factor incorporates judgments about the amount of information on the toxicity of the compound, the differences between body sizes and weights between adult males and children, and an assumption about the relative contribution of the compound to the total exposure from air. The total uncertainty factor in the case of acetaldehyde was 36768.9.

The State of Massachusetts used a multistage model of carcinogenesis to calculate a unit risk for carcinogenic potency, using the data on male rat nasal adenocarcinoma-type tumours in rats from Woutersen *et al.* (1986). This treatment group and tumour site were considered to be the most sensitive. Only the data from low and middle-dose groups were used because of the poor statistical fit to the multistage model when the high dose group was included. A unit risk of $2.26*10^{-6}$ tumours/($\mu g/m^3$) was reported. For $1*10^{-5}$ and $1*10^{-6}$ additional cancer risk levels, this corresponds to air concentrations of 4.4 $\mu g/m^3$ and 0.44 $\mu g/m^3$, respectively, for lifetime exposure.

9. Key Risk Management Considerations:
The primary objective of the process is the protection of public health. The Massachusetts system uses hazard assessment only and does not use the number of exposed individuals as a criterion for regulatory action. Furthermore, the selection of the AAL is based on the most sensitive effect. Massachusetts developed their own cancer unit risk value (Commonwealth of Massachusetts, 1990) and adopted the ACGIH occupational TLV values for regulation development purposes. For carcinogens, a maximum allowable increase in risk associated with exposure to a chemical was set at one per million ($1*10^{-6}$) for a 70-year lifetime.

10. Multimedia Considerations of Guidelines:
A generic allowance was made for contributions from sources other than respiration: "A relative source contribution factor of 20% is also included to account for sources other than air." (Commonwealth of Massachusetts, 1990, pg. viii).

11. Other Relevant Factors:
No information.

7.8 Adverse Effects of Formaldehyde and Acetaldehyde on Nasal Mucosa

The nasal toxicity of inhaled formaldehyde and acetaldehyde are very similar. Qualitatively, both acetaldehyde and formaldehyde are electrophilic compounds. Both compounds can react with the amino groups of nucleic acids and the sulfhydro groups of protein. These two compounds have been shown to have the following effects in human cultured cells or animal nasal mucosa preparations: formation of cross-linked envelopes, levels of cytosolic calcium, DNA-protein cross-links, DNA strand breaks and on the DNA repair enzyme - O^6-methylguanine transferase, colony-forming efficiency and clonal growth rates in cell cultures (Saladino *et. al.*, 1985; Lam *et. al.*, 1986; Dellarco, 1988; Grafström, 1990; Grafström *et. al.*,1994). The genotoxic properties of these two compounds are similar but different in the "genotoxicity ranking" in that formaldehyde ranks higher than acetaldehyde (see Morris, *et. al.*, 1996)[2].

It should be emphasized that both acetaldehyde and formaldehyde exhibit contact-site specific toxicity and the toxicity profiles for these two compounds are remarkably similar. In animals, vapour of either compound induces damages to the upper respiratory tract, e.g. short-term inhalation exposure caused inflammation and degeneration of the nasal mucosa and long-term exposure promoted formation of nasal squamous cell carcinoma and adenocarcinoma whereas other organs were not appreciably affected (Woutersen *et. al.*, 1982; Woutersen *et. al.*, 1987; Grafström, 1990; Grafström *et. al.*,1994). The contact site specificity is consistent with the metabolic profiles of acetaldehyde and formaldehyde. Morris *et. al.* (1996) suggest that the cytotoxicity and tumours may develop at inspired burdens which approach or overwhelm nasal detoxification. For example, inhaled formaldehyde at 14.3 ppm (26 mg/m^3) elevated nasal tumour rates significantly in animals but did not clearly raise tumour rates at 5.6 ppm (10 mg/m^3). During the 6-hour daily exposures, these two inspired concentrations corresponded to delivered dose rates of 4 and 1.6 µg/min, respectively. The total nasal detoxification capacity for formaldehyde is roughly 3 µg/min (V_{max} for formaldehyde and aldehyde dehydrogenases combined). Inhaled acetaldehyde at 750 ppm (1350 mg/m^3) induced nasal tumour formation significantly (despite lower doses were not tested). This dose corresponds to a delivered dosage rate of 90 µg/min. The nasal detoxification capacity for acetaldehyde is approximately 70 µg/min (combined isozymes). However, it should be noted that the dosimetry for inspired concentrations and delivered dosages may not follow a linear relationship (due to decreases in deposition efficiencies with increasing exposure concentrations) and species specific variations also exist (Morris, 1997). It has been found that in mouse, rat, hamster and guinea pig, the delivered dosage rate at an inspired concentration of 1000 ppm (1800 mg/m^3) exceeds the metabolic capacity of aldehyde dehydrogenase of the nose; however, at an inspired concentration of 100 ppm (180 mg/m^3), the mouse, hamster and guinea pig, but not the rat, may exceed the metabolic capacity of the nose (Morris, 1997). Therefore, the suggestion that "the cytotoxicity and tumours may develop at inspired burdens which approach or overwhelm nasal detoxification" should be

[2] Additional references for this Section for the structural activity relationship between acetaldehyde and formaldehyde can be found in Morris *et. al.*,1996.

considered with caution when studying the dose-response relationship for acetaldehyde (Morris *et. al.*1996).

Both acetaldehyde and formaldehyde are metabolized to nontoxic formic acid and acetic acid respectively, by aldehyde dehydrogenase. Aldehyde dehydrogenases are distributed ubiquitously in animals and humans. It has been estimated that the total aldehyde dehydrogenase activities (isozymes of low and high affinity combined) in the gastric mucosa of the human stomach is about 13000 mg/day. An individual may consume as much as 75 to 200 mg of acetaldehyde in a day through food ingestion and likely consumes less than these amounts for formaldehyde (Feron *et. al.*, 1991; IARC, 1995; Morris *et. al.,* 1996). It would appear that normal daily diet intake of acetaldehyde and formaldehyde may not contribute to toxic levels for these aldehydes in humans (although the actual metabolic capacity will be dependent upon the amount of the aldehydes ingested and the particular isozymes activated by those dietary levels). On the other hand, inhaled acetaldehyde and formaldehyde are capable of inducing site specific damages to the nasal tissues of animals, studies on the relative potency of toxic effects for these two compounds can be achieved using nasal damage and tumour rate as indicators. (See Table 3 in text for a summary of comparing the dosimetry and nasal toxicity for acetaldehyde and formaldehyde.)

.

Working on the basis of cyclic flow conditions and estimates of deposition efficiency for acetaldehyde and formaldehyde in the nasal cavity, the total delivered dosage rate for these two compounds could be calculated. Using the delivered dose estimates, the toxicity of acetaldehyde and formaldehyde on the induction of squamous cell carcinoma, adenocarcinoma, total carcinoma, cytotoxicity of nasal tissues as well as ability to elicit formation of DNA-protein cross-links in animals were compared (see Table 3 in text) (Morris *et. al.,* 1996). Acetaldehyde would appear to be approximately 21-fold less potent than formaldehyde to induce squamous cell carcinoma in the nose (delivered dose for acetaldehyde, 4.4 mg/cm^2/day vs for formaldehyde, 0.21 mg/cm^2/day). Adenocarcinoma may not be a suitable candidate for comparison since formaldehyde-induced adenocarcinoma formation is not a specific effect for this compound, possibly because of the high detoxification pattern for formaldehyde at the posterior nasal cavity where olfactory epithelium exists. However, using total carcinoma incidence rates (% of squamous cell carcinoma plus % of adenocarcinoma), assuming total tumour incidence follows a linear fashion, an estimate of a 50% "toxic dose" can be obtained for acetaldehyde (2.9 mg/cm^2/day); formaldehyde at 0.21 mg/cm^2/day induced a 47% total tumour incidence. The relative potency for acetaldehyde/formaldehyde can be projected to be 14 (14-fold less potent for acetaldehyde at 2.9 mg/cm^2/day as compared with formaldehyde at 0.21 mg/cm^2/day).

Based on the LOAEL/NOAEL for nasal cytotoxicity induced by subchronic exposure to acetaldehyde or to formaldehyde, the relative potency for acetaldehyde vs formaldehyde can be estimated to be 28-fold less potent for acetaldehyde (acetaldehyde 1.2 mg/cm^2/day *vs* formaldehyde 0.043 mg/cm^2/day).

On the basis of DNA-protein cross-link formation in the respiratory mucosa, acetaldehyde appears to be 34-fold less potent than formaldehyde (at 4-5% formation; acetaldehyde, 2.9 mg/cm^2/day vs formaldehyde, 0.084 mg/cm^2/day).

It is apparent that on a delivered dose basis, acetaldehyde is 14- to 34-fold less potent than formaldehyde to induce carcinogenic and noncarcinogenic damages to nasal tissues of animals. Similar phenomenon is observed in tissue preparations or cultured cells that acetaldehyde is less potent than formaldehyde to elicit cellular events, such as clonal cell growth, cross-linked envelope, DNA-protein cross-links and DNA single strand breaks (Krokan *et. al.,* 1985*;* Saladino *et. al*., 1985; Lam *et. al.,* 1986; Dellarco, 1988; Grafström *et. al*., 1994).

7.9 Summary of Mutagenicity Assessment for Acetaldehyde

In vitro Mutagenicity Assays for acetaldehyde in animal or human tissues

Assay	Strain/type	S9 Activation	Dose	Results	Observations	Reference¶
			Studies reported in WHO (1995)			
Sister chromatid exchange	human peripheral lymphocytes, Chinese Hamster Ovary (CHO) cells, mouse lymphoma L5178Y cells			positive		Thilagar *et. al.* (1984 a,b)
Sister chromatid exchange	CHO cells	with or without S9	0-5000 µg/mL	negative	standard (25-29 hour after treatment) harvest time	Anderson *et. al.* (1990)
Sister chromatid exchange	CHO cells	with or without S9	0-15 µL/mL	negative		Thilagar & Kumarco (1983)
Sister chromatid exchange	CHO V79 cells		0-4%	?	marginal (<2-fold), reproducible increases in frequency; not dose-related	Jongen *et. al*. (1981)
Chromosome aberration	human peripheral lymphocytes, Chinese Hamster Ovary (CHO) cells, mouse lymphoma L5178Y cells		not stated	positive		Thilagar *et. al.* (1984 a,b)
Chromosome aberration	CHO cells	with or without S9	0-15 µL/mL	positive	dose-dependent increase	Thilagar & Kumarco (1983)
Chromosome aberration	CHO cells	with or without S9	0-5000 µg/mL	negative	standard (10-14 hour after treatment) harvest time	Anderson *et. al.* (1990)
Cells *in vitro*	CHO cells		0.5-5% v/v	negative	forward mutation to 6-thioguanine resistance; mutation rate was corrected for survival	Jongen *et. al*. (1981)

Assay	Strain/type	S9 Activation	Dose	Results	Observations	Reference¶
Cells *in vitro*	Epithelial cells (V79)	without S9	0, 35000-141000 mg/m^3 (4 concentrations for 1 hour); expression time of 6 days	negative	varying the expression time was reported to have no effect; cell survival was reduced by about 20% at 141000 mg/m^3	Jongen *et. al*. (1981)
Cell mutation	L5178Y mouse lymphoma		not stated	negative		Thilagar *et. al.* (1984a,b)
Cell mutation	L5178Y mouse lymphoma	with or without S9	0-3000 µL/mL	positive and negative	overall questionable evaluation of activity	Myhr *et. al.* (1990)
Cell transformation	primary Syrian hamster embryo cells		0.5 mL/4.6 L chamber	positive	enhanced transformation by SA7 adenovirus	Hatch *et. al*. (1983)
HGPRT-deficient	Chinese hamster V79 cells		0-4%	negative		Jongen *et. al*. (1981)
Micronucleus	Chinese hamster V79 cells		not stated	negative		Gu & Wang (1988)
Unscheduled DNA synthesis	primary rat hepatocytes		not stated	negative		Trueman *et. al.* (1987)
Unscheduled DNA synthesis	primary rat hepatocytes		not stated	positive & negative		Thilagar *et. al.* (1984a)
Cell transformation	BALB/C-3T3 mouse		0.01%	negative		Price *et. al.* (1978)
Cell transformation	C3H-10T1/2 CL8 mouse		not stated	negative		Thilagar *et. al.* (1984a)
Unscheduled DNA synthesis	primary rat hepatocytes			positive & negative	a “marginal” positive result reported	Thilagar *et. al.* (1984a)
Unscheduled DNA synthesis	human lymphocytes	with or without S9	2.5 - 10 µL/mL	negative		Perocco & Prodi (1981)
Unscheduled DNA synthesis	Chinese hamster V79 cells		0 - 5%	negative		Jongen *et. al.* (1981)

Assay	Strain/type	S9 Activation	Dose	Results	Observations	Reference¶
DNA repair synthesis	primary rat hepatocytes		0.7 - 16 mM	negative		Andrae & Wolff (1983)
			Studies reported in Dellarco (1988)			
Gene mutation	nematodes	without S9	18 and 178 mM	positive	mutations affecting egg-laying; positive at 18 mM and no dose relation	Greenwald and Horvitz (1980)
Sex-linked recessive lethal	Drosophila		22500 ppm (injection of adult males; all germ cells stages treated); 25000 ppm (feeding)	positive and negative	positive at 22500 ppm; negative at 25000 ppm	Woodruff *et. al.* (1985)
Chromosome aberration	Drosophila		22500 ppm (injection of adult males; all germ cells stages treated)	negative	heritable translocation	Woodruff *et. al.* (1985)
Chromosome aberration	rat skin fibroblast	without S9	a) 0.1 - 10 mM for 12, 24, 48 hours; b) 0.01 - 1 mM for 12 and 24 hour	a) positive b) positive	a) dose response observed; lowest effect concentration tested: 0.5 mM (1.9% micronuclei at 12 hour and 1.1% micronuclei at 24 hour) b) gaps, breaks, exchange-type aberrations, acentric fragments; 1 mM (12% aberrant cells at 12 hour), 0.1 mM (16% aberrant cells at 24 hour); questionable positive results for aneuploidy)	Bird *et. al.* (1982)

Assay	Strain/type	S9 Activation	Dose	Results	Observations	Reference¶
Chromosome aberration	human lymphocytes	without S9	0.18 and 0.36 mM for 24 hours	positive	gaps, breaks, exchange-type aberrations in Fanconi anemia cells, not detected as clastogenic in normal lymphocytes at same dosages	Obe *et. al.* (1979)
Chromosome aberration	human lymphocytes	without S9	0.09 - 1.08 mM 72 for hours	positive	dose response observed; gaps, breaks exchange-type aberration; 0.72 mM (17% aberrant cells)	Böhlke *et. al.* (1983)
Chromosome aberration	whole animal: female rats and treated embryos		0.02 mL of 178 mM intra amniotically	positive	gaps and breaks; 178 mM (12% aberrant cells)	Barilyak and Kozachuk (1983)
Sister chromatid exchange	CHO cells	without S9	0.09 and 0.18 mM for 8 days	positive	dose response relationship observed; 0.09 mM (9 SCE/cell)	Obe and Ristow (1977)
Sister chromatid exchange	CHO cells	without S9	0.045 - 0.27 mM for 24 hours	positive	dose response relationship observed; 0.09 mM (10 SCE/cell)	Obe and Beck (1979)
Sister chromatid exchange	CHO cells	with and without S9	0.18 - 1.8 mM plus S9; 0.18 - 0.89 mM minus S9	positive	0.89 mM (28 SCE/cell plus S9 and 41 SCE/cell minus S9)	de Raat *et. al.* (1983)
Sister chromatid exchange	human lymphocytes	without S9	0.09 - 0.36 mM for 24 hours	positive	dose response relationship observed; 0.18 mM (6 SCE/cell)	Ristow and Obe (1978)
Sister chromatid exchange	human lymphocytes	without S9	0.36 - 1.8 mM for 3 hours	positive	the presence of aldehyde dehydrogenase + NAD slightly reduced the response); 0.36 mM (7-15 SCE/cell)	Obe *et. al.* (1986)

Assay	Strain/type	S9 Activation	Dose	Results	Observations	Reference¶
Sister chromatid exchange	human lymphocytes	without S9	0.09 - 0.18 mM for 90 hours	positive	dose response relationship observed; 0.18 mM (11 SCE/cell)	Jansson (1982)
Sister chromatid exchange	human lymphocytes	without S9	0.09 - 1.08mM for 72 and 96 hours	positive	dose response relationship observed; 0.18 mM (8 SCE/cell)	Böhlke *et. al.* (1983)
Sister chromatid exchange	human whole-blood lymphocyte cultures	without S9	0.063 - 2 mM for 48 hours	positive	0.25 mM (7 SCE/cell)	Norrpa *et. al.* (1985)
Sister chromatid exchange	human lymphocytes	without S9	0.1 - 0.3 mM for 72 hours; 0.6 - 2.4 mM for 1 hour	positive	dose response relationship observed; 0.1 mM (about 20 SCE/cell); 2.4 mM (about 18 SCE/cell)	He and Lambert (1985)
Sister chromatid exchange	Whole male CBA mice		2.5E-7 and 5E-7 mole/kg; i.p. injections	positive	almost doubled background frequency at 5E-7 mole/kg (1 mouse/treatment; no sham-treated control)	Obe *et.al.* (1979)
Sister chromatid exchange	male and female Chinese hamsters		2.3E-7 - 1.1E-5 mole/kg; i.p. injections	positive	almost doubled background frequency at 1.1E-5 mole/kg	Korte and Obe (1981)
DNA strand breaks	rat hepatocyte cultures	without S9	0.03 - 3 mM for 3 hours	negative	no single-strand breaks	Sina *et. at.* (1983)
DNA strand breaks	human lymphocytes	without S9	10 mM for 4 hours	negative	no single-strand breaks	Lambert *et. al.* (1985)
DNA strand breaks	human bronchial epithelial cells	without S9	up to 1 mM for 1 hour	negative	no DNA damage; no DNA-protein cross-links	Saladino *et. al.* (1985)

Studies cited in the present document

Assay	Strain/type	S9 Activation	Dose	Results	Observations	Reference¶
DNA strand breaks	human bronchial epithelial cells		3 - 100 mM for 1 hour	negative	3 mM (inter-strand cross-link occurred; dose-related); 10 mM (DNA-protein cross-link observed; dose-related)	Grafström *et. al*. (1994)
DNA strand breaks	human lymphocytes		0 - 100 mM for 1 hour	positive	1.56 mM (single-strand break); 100 mM (double strand break)	Singh and Khan (1995)
6-Thioguanine (6-TG) induction	human skin fibroblasts		3 - 10 mM for 5 hours	positive	biphasic peaked at 5 mM to a frequency of 150 per 10^6 survivors (background frequency: 1- 5 per 10^6 cells.	Grafström *et. al*. (1994)
Sister chromatid exchange	human lymphocytes		0.2 mM for 24 - 96 hours	positive	SCE/cell increased about 4 times over control	Lambert and He (1988)
Chromosome aberration	Chinese hamster embryo cells		0.45 mM - 1.36 mM	positive	0.9 mM (chromosome aberration); 0.45 mM (aneuploidy-mainly increase of hypodiploidy)	Dulout and Furnus (1988)

Note ¶ for references cited in WHO (1995) and Dellarco (1988), see these two review documents for details of original references.